University of Toronto
MEDICAL JOURNAL
VOL LXIII No.3

Feature Article:
Autoimmunity In Endocrine Disease

M D I C L® INC.

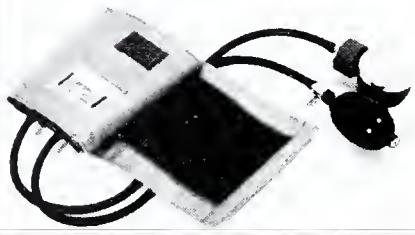
MDICL INC., introduces the latest in medical Electronics: ECG'S, ECG ANALYZERS, Monitors, Computerized Spirometers and much much more. Also a complete line of disposable and medical supplies at the most competitive prices.

MDICL INC.
175 TORYORK DRIVE, UNIT 6
WESTON, ONTARIO M9L 2Y7
TEL: 416-747-1125
TLX NBR: 06-23096 MDIC TOR

DEDICATED TO THE MEDICAL PROFESSION

SPECIAL FOR MEDICAL STUDENTS, DOCTORS ETC.

ANEROID SPHYGMOMANOMETER WITH POUCH



ONLY $9.99

DELUXE DUAL SIDED STETHOSCOPE

ONLY $5.99

DELUXE STAINLESS STEEL DUAL SIDED STETHOSCOPE

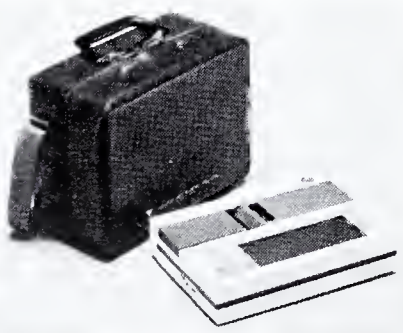
ONLY $14.99

SPRAGUE RAPPAPORT TYPE STETHOSCOPE

ONLY $15.99

THE HEART OF EVERY PRACTICE. MAKE IT YOURS.

FULLY AUTOMATIC PORTABLE ECG'S FROM FUKUDA M-E. MODEL CARDISUNY 501 A-B



WEIGHT: 1.5 Kg —
Size 24 × 17.5 × 4.8 cm.

Introducing the World's finest fully automatic, most compact and easy to use full 12-lead ECG. By the touch of a membrane key, it provides you in merely 45-seconds with a complete 12-lead trace. Ideal for use by: Doctors, Clinics, Hospital wards, Laboratories, Nursing Homes, house call or anywhere you require an ECG. A slick liquid crystal display keyboard contains all controls that are sealed to insure dust free & trouble free operation. Available in 3 ways: Dry cell, Dry cell adaptor combination, NICD Recharger, your choice. And the price is even more convincing.

FREE: LUXURIOUS CARRYING CASE FOR EASE OF STORAGE AND PORTABILITY

FULLY AUTOMATIC COMPUTERIZED SPIROMETERS FROM FUKUDA SANGYO

FUKUDA, the world's pioneers in the spirometry field for over 45 years, introduces a new generation of sophisticated spirometers: MODELS ST-100 and ST-200. Featuring the latest in micro-processor technology, instant LCD visual diaplay, instant graphic printout of all parameters & respiration waveforms. Its compact in design, portable and extremely simple to use. A carrying case is also available. A marvel of computer age technology. A classic HI-TECH...

Ideal for use in Hospital, Doctors offices, Clinics, Nursing Homes and Industries where high pollution is inherent.

COMPLETE YOUR PRACTICE WITH THESE MUST HAVE MODERN AGE EQUIPMENT.

COME VISIT OUR SHOWROOM. WE WILL ASSIST YOU IN SETTING-UP YOUR COMPLETE OFFICE WITH THE LATEST MEDICAL FURNITURE, EQUIPMENT & SUPPLIES. WE ARE YOUR ONE STOP MEDICAL SUPPLIER. WE WILL STRIVE TO ACHIEVE YOUR BEST POSSIBLE RESULTS. WE WILL DEFINITELY NOT EXTRA BILL YOU!

ALL OUR PRODUCTS CARRY A ONE YEAR WARRANTY. ORDERS OVER $300.00 ARE PREPAID. UNDER $300.00 PLEASE ADD $10.00 FOR SHIPPING & HANDLING. VISA & MASTER CHARGE ARE WELCOME. FINANCING AVAILABLE. VISA & MASTER CARD ARE ACCEPTED. CALL TODAY FOR YOUR ORDERS OR PLEASE WRITE US FOR FURTHER INFORMATION.

University of Toronto
MEDICAL JOURNAL
Established 1923. An Undergraduate Publication Volume 63, Number 3, May 1986

Editorial

This is the last issue of *The University of Toronto Medical Journal* for the year 1985-86. We have enjoyed being the editors of this year's Journal and we hope you have enjoyed the variety of topic which we have covered. We entend our welcome to next year's editorial staff. We wish to thank this year's editorial staff, writers and publisher for their contributions.

The theme of this last issue is autoimmunity, an area of research that is receiving much contemporary interest. Our feature article, for this issue is *Autoimmunity in the Endocrine System* by Dr. Robert Volpé, Physician-in-Chief at the Wellesley Hospital and Professor of Medicine at the University of Toronto.

We have also included an article on the much debated subject midwifery. Our writer, Vivian Rushworth, advises us that there has been changes in the legislature of midwifery since she wrote the article.

We wish to thank all readers for their continuing support of *The Journal.*

The Editors

Contents

Editorial 1

Autoimmunity In Endocrine Disease
Robert Volpé 3

The Influence Of Soft Tissue Coverage Of The Healing Of Tibial Fractures
Rex Verschuren 20

Management Of Meniscal Cysts By Arthroscopic Surgery
Jay S. Wunder 28

Respirology Rounds
Poenaru, Hyland, Jones, Gray 32

A Model Of Pulmonary Hypertension in Dogs
D. Gluckman, J.D. Cooper 35

Canadian Midwifery Reborn
Vivian Rushworth 41

Patrons 45

Infective Endocarditis: A Clinic and Pathological Study
Richard Upenieks, Jagdish Butany 46

Review:
Doing Right; Doctors; The Broken Brain
K. Watts, P. Stewart, R. Mounsey 49

Editorial Staff

Editors-in-chief:
Warren Mason, 8T7
Pamela Stewart, 8T7

Associate Editor:
Dan Poenaru, 8T6

Editorial Board:
Eva Chow, 8T7
Ed Etchells, 8T7
Lydia Hoh, 8T7
Mahmood Kara, 8T8
James Kim, 8T9
Susan Knabe, 8T7
Gabor Lantos, 8T7
Ann Li, 8T7
Robert Mounsey, 8T8
Anysia Rusak , 8T9
Michael Wong, 8T9

Medical Alumni Association

• **THE MEDICAL ALUMNI ASSOCIATION** is the bridge between the graduates and the Faculty of Medicine, University of Toronto.

• The Association provides financial assistance (scholarships, bursaries, travel grants, fellowships loans) for undergraduates, as well as sponsoring programs that are of particular Interest — General Practice Panel, Arts and Letters Committee, Undergraduate Affairs, Graduation Banquet, etc.

• At the Faculty level, there are two representatives on the Faculty Council, a representative on the Admissions Committee, and the Chairman of the Student Aid Committee is a representative on the Student Awards Committee.

• At the University level, the Association has two representatives on the Universtiy of Toronto Alumni Association, two representatives on the College of Electors, and a representative on the Varsity Fund Executive Committee.

• We are also represented on various Search Committees when Department Chairmen and the Dean of Medicine are being sought.

• The Association is also involved in providing some impetus to five year reunions. Two letters will be sent free of charge, for each class celebrating their reunion. Every attempt is made to keep an up-to-date address list of all our graduates. Please remember to notify YOUR Medical Alumni Association of any address change.

• The Association is governed by graduates who give their time and talent voluntarily. There is one full time employee. Donations given for Student Aid are used entirely for that purpose. Trust funds are administered, without charge, following the direction of the donor.

Autoimmunity In Endocrine Disease

Robert Volpé, M.D. FRCP (C), FACP

Professor, Department of Medicine
University of Toronto
Physician-in-Chief, The Wellesley Hospital,
Toronto, Ontario, Canada

Introduction

In order to comprehend autoimmune diseases, it is necessary to become familiar with general[1] principles of immunity. This section will briefly describe these principles, and then summarize some important elements of each of the autoimmune endocrine diseases (Table 1). Shortage of space does not permit more than the most brief account of these disorders and the interested reader is referred to relevant reviews.[1 2 3]

Immunity may be defined as a physiological mechanism of the organism making it capable of recognizing substances that are foreign and of neutralizing, eliminating or metabolizing them without injury to its own cells.[4] While such responses may be specific and non-specific, specific immunological responses are restricted primarily to chordates. Immunology is the biological field that allows living organisms to distinguish "self" from "non self" and to eliminate the latter. It thus deals with antigens, antibodies, and their interactions, cells that directly or indirectly control and/or synthesize antibodies, humoral substances that participate in immunological processes, and genetic mechanisms that control the immunological status of organisms.

An antigen is a substances that induces the production of antibody by an organism and reacts with it. Antigens may either by proteins, polysaccharides, glycoproteins, lipoproteins or lipopolysaccharides, all of which have antigenic properties. Some low molecular weight substances which cannot themselves activate the immune system may become able to do so after attachment to antigenic compounds (haptens). The immune response depends on the orchestrated interaction of three types of cells, the macrophages, the T lymphocytes and the B lymphocytes. The macrophages process the antigens and present them in immunogenic form to lymphocytes. They also phagocytize and pinocytize various cells and foreign substances. Macrophages also activate special subsets of T lympocytes, which in turn trigger a toxic reaction via the synthesis and excretion of certain humoral substances such as interleukin

All lymphocytes are derived from the bone marrow. However, about 55% are processed in the thymus by various thymic hormones to become differentiated thymic-dependent (T) lymphocytes. The remainder are processed in the micro-environment of the bone marrow itself to become lymphocytes that are analagous to those derived from the bursa of Fabricius in birds (and are thus termed bursa-equivalent or B lymphocytes). The development of the immune system which allows the specific response to specific antigens is of importance. The repertoire of T and B lymphocytes which is capable of interacting with virtually every possible antigen with which the cells may come in contact must occur via mutation of the original complement of lymphocytes so as to produce large numbers of new clones of cells, each capable of interacting with a specific antigen. This point will be discussed further below.

Production of antibodies (by B lymphocytes) is usually under the direct control of helper T lymphocytes. When antigens or mitogens stimulate T lymphocytes, they grow, divide and secrete low molecular weight proteins termed lymphokines. Lymphokines play a role in cell mediated immunity including resistance to tumour cells, viruses and foreign mammalian cells (graft rejection). Special lympho-

Table 1. Autoimmune endocrinopathies and those Nonendocrine Organ-Specific Autoimmune Disorders Associated with them.

Endocrinopathy	Disease
Graves' (Basedow's, Parry's Disease)	Pernicious anemia
Hashimoto's thyroiditis	Vitiligo
Idiopathic Addison's disease	Myasthenia gravis
Insulinopenic diabetes mellitus	Sjogren's syndrome
Autoimmune oophoritis and orchitis	Rheumatoid arthritis
Autoimmune hypoparathyroidism	Idiopathic thrombocytopenic purpura
Autoimmune hypophysitis	Chronic active hepatitis
Some cases of infertility due to antisperm antibodies	Primary biliary cirrhosis

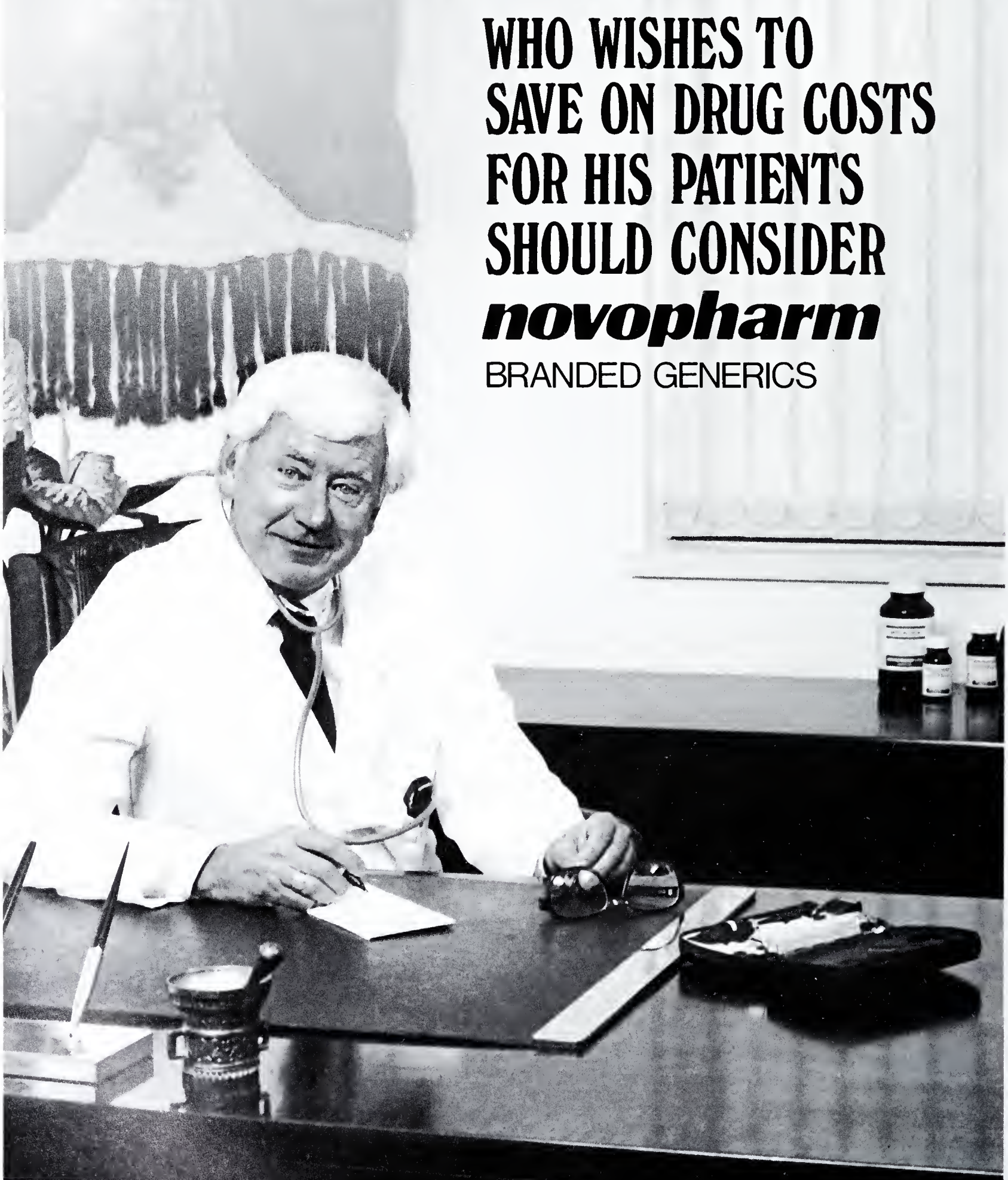
Reproduced with permission from Volpe[2]

THE CONCERNED PHYSICIAN

WHO WISHES TO SAVE ON DRUG COSTS FOR HIS PATIENTS SHOULD CONSIDER

novopharm

BRANDED GENERICS



novo-methacin Indomethacin
novo-naprox Naproxen
novo-pranol Propranolol HCl
novo-triamzide Triamterene-Hydrochlorothiazide

novopharm ltd.
1290 Ellesmere Road, Scarborough, Ontario, Canada M1P 2Y1
Telephone: (416) 291-8876

PAAB CCPP

THE LARGEST CANADIAN OWNED COMPANY SPECIALIZING IN BRANDED GENERIC PHARMACEUTICAL PRODUCTS

kines activate synthesis of antibodies by B lymphocytes. T lymphocytes are also responsible for cell mediated, delayed hypersensitivity reactions. According to our current concepts, Tlymphocyte-dependent antibody production occurs via the following steps:

1) Antigen is taken up and processed by macrophages, which have DR(Ia) antigenic determinants;
2) Antigen is presented in immunogenic form to specific T helper lymphocytes;
3) Differentiation and coexpansion of effector T helper cells takes place
4) T helper lymphocytes deliver their message to antigen-specific B lymphocytes
5) Differentiation and coexpansion of effector B lymphocytes takes place. In the case of autoimmune disease, to be discussed below, after the immune assault has been mounted, antigen presentation (via Ia expression) can occur secondarily directly via the target cells themselves.

(a) T lymphocytes

Thymus dependent (T) lymphocytes recognize antigens and possess antigen specific receptors. They may be functionally divided into helpers, suppressors, cytotoxic cells and effectors in delayed hypersensitivity. They do not, however, produce antibody into the circulation. T lymphocytes participate in cellular and humoral immunity, composed of a complex series of interactions between antigen-presenting macrophages, T lymphocytes and B lymphocytes. Immunological balance depends on normal communication between the cells which in turn depends upon the recognition of self determinants displayed by immunocompetent cells. Two major groups of determinants participate in these communications: products of genes (surface glycoproteins) localized in the major histocompatibility complex (MHC) on chromosome[6], and determinants made of aminoacid sequences in the antibody-combining site of immunoglobulin molecules (idiotypic determinants). It has been suggested that for each antigenic determinant with which an organism will come into contact, there exists a clone of B lymphocytes expressing an immunoglobulin (Ig) molecule with a specific idiotypic aminoacid sequence specific for that antigen. T lymphocytes also possess antigen-specific receptors composed of a variable part of the Ig heavy chain that binds to antigen.

Several antigens on the T lymphocyte surface have become useful markers for recognizing and purifying T cells and their subsets. Using increasingly specific monoclonal antibodies in various fluorescent combinations it is now possible to divide T lymphocyte subsets into suppressors, cytotoxic, helpers and inducers. Certain T lymphocytes also have a surface receptor for Ia proteins. Transformation of T lymphocytes is associated with the response of such cells to HLA-DR (Ia) proteins on B lymphocytes when they are co-cultured (the mixed lymphocyte reaction, MLR). T lymphocyte transformation can also occur as a result of the interaction of T lymphocytes with certain mitogens.

Helper T lymphocytes

Antigens that are T-cell dependent are usually more complex than T-cell-independent antigens, which may stimulate B lymphocytes without the participation of T lymphocytes. To respond to T cell dependent antigens, the B lymphocyte must be triggered by two signals, one from the antigen and the second from the T lymphocyte. Human helper T lymphocytes represent 40-60% of peripheral blood T lymphocytes, whereas suppressor T lymphocytes compose about 5-15% of circulating T lymphocytes.

Suppressor T lymphocytes

Suppressor T lymphocytes represent important immunoregulatory cells. There appear to be two types of suppressor T lymphocytes, one acting on helper T lymphocytes (level one suppression) while the other regulates (suppresses) the generation of contra-suppression as well. It would appear that the main mechanism of tolerance is represented by specific and non-specific suppressor T lymphocytes.[1 4] If a helper T lymphocyte specific for an autologous tissue arises, it must be suppressed if autoimmune disease is not to occur. It is this normal mechanism which is essential for the suppression of autoimmune phenomena. Minor dysfunction of specific suppressor T lymphocytes under ideal circumstances, would not be accompanied by any overt clinical disorder although perhaps by serological expression (the appearance of antibodies in the plasma). Variations in generalized suppressor T lymphocyte function occurring during life brought about by adverse influences acting on suppressor T lymphocytes such as infections, stress, drugs and aging might add to the antigen-specific abnbormality, leading to variations in its expression.[5]

(b) Theories of antibody production

The Burnet theory of antibody production relates to the genetic endowment of the lymphocytes with the capability of synthesizing immunoglobulins. When unstimulated by antigen, only small amounts of immunoglobulin are made. On exposure to the corresponding antigen, lymphocytes start to reproduce and differentiate into the clone of immunoglobulin secreting plasma cells. The resulting clone of cells consists of a large population and the antibody produced becomes measurable in the blood. The genetics of the immunoglobulin response have led to two theories, namely, the germ line theory which postulates the existence of one gene for each peptide in an immunoglobulin. The somatic mutation theory is based on the recognition of a constant amino acid sequence of the C domain of the immunoglobulin, but variability of the V gene. When the immunoglobulin reacts with some antigen on the cell surface, cell proliferation and clone formation would follow. The probability that such specific immunoglobulin would be present when an antigen is injected is quite high considering normal mutation rates.

(c) Antibodies

The most important products of B lymphocytes are antibodies. These are immunoglobulins synthesized in response to antigenic stimulation. They combine with antigen through their antibody sites in a "lock and key fashion" whereas a distinct region of the molecule is responsible for effector functions such as complement activation, cytophilic activity, control of catabolic rates, and transfer across specialized

membranes. Five distinct classes are characterized by their unique antigenic specificity (isotype) namely: IgG, IgA, IgM, IgD and IgE. IgG is the predominant class of immunoglobulin in normal serum, and accounts for most of the autoantibodies which are important in the present account. Other types of Ig will not be discussed.

(d)Tolerance

The mechanism of self-tolerance must be mentioned here. This signifies that the organism is immunologically unresponsive to his/her own tissues. Such a condition may occur when responses to other antigens are normal. The mechanisms of induction and maintenance of tolerance are poorly understood; exposure to antigen in fetal life by a variety of mechanisms such as clonal abortion or deletion, impairment of suppressor T lymphocytes, modulation or paralysis of receptors by antigens, overstimulation and exhaustion of clones, or a combination of these may be involved. Factors predisposing to tolerance include immaturity or damage to the immune system and certain properties of the antigens. Among the former, genetic factors in the host, exposure to fetal or neonatal antigens and chemical or physical manipulation, should be mentioned.

In normal organisms, the immune system remains as a counter to autoimmune disease by virtue of a finely tuned balance between various subsets of lymphocytes, particularly helper T lymphocytes and suppressor T lymphocytes. Several theories have been advanced to explain autoimmune processes.[7] These include the appearance of self antigens to which the lymphocytes have not been previously exposed (sequestered antigen theory); the altered antigen theory whereby environmental factors such as viruses, radiation etc. may modify or alter body constituents so as to render them non-recognizable as self and therefore antigenic; the forbidden clone theory whereby a mutant effector lymphocyte arises and is not destroyed by normal immune regulatory mechanisms; and finally defective immune regulation, the most likely cause of the autoimmune endocrinopathies.[1 4]

(e) Genetic factors

The disturbance in immunoregulation which leads to autoimmune endocrine diseases is clearly genetic in part, and this genetic factor renders the bearer susceptible to the disease; the autoimmune endocrine diseases tend to aggregate in families, and more than one of these disorders tend to co-occur within the same patients. It is also clear that the mode(s) of inheritance of these diseases do not follow simple genetic rules. The finding that the autoimmune endocrinopathies occur preferentially in individuals who have inherited certain HLA markers definitely establishes that genetic factors are involved in the development of these disorders.[8 9]

(f) HLA System

The HLA system was originally discovered as a leukocyte blood group system; it soon became obvious that this system is the human major histocompatibility complex (MHC) that to a considerable degree determines the fate of transplanted organs. However, in 1969 it was demonstrated that these complexes contained so-called immune response (Ir) and most probably immune suppressor (Is) determinants; these control the ability of the individual to respond immunologically, when exposed to various "foreign" antigens.10 Distinction should be made between the three major classes of MHC factors: Class I antigens which are membrane bound surface molecules present on most cells of the body; Class II antigens which are bioichemically different cell surface molecules found only on certain cell types, and Class III factors which comprise some of the components of the complement cascade. All MHC characters are controlled by genes located at a number of loci very close to each other on one of the autosomal chromosomes. For example, the HLA loci lie within a few centimorgans (cross over units) of each other on the short arm of chromosome.[6] (Fig. 1). Discussion will focus primarily on Class II MHC antigens (HLA-DR) since they appear to have the most significant correlation with autoimmune endocrine diseases. Most patients with such diseases have the appropriate HLA marker (Table 2); the possession of such a marker increases the relative risk of the disease several fold, but leaves the vast majority of persons with this particular marker to remain free of the disease for their lifetime. It thus seems evident that the markers noted in Table 2 are not the true genes responsible for disease susceptibility.

Table 2. Associations Between HLA and Autoimmune Endocrinopathies and Some Related Disorders.

Condition	HLA	Frequency (%) Patients	Controls	Relative risk
Idiopathic Addison's disease	D/DR3	69	26.3	6.3
Graves' disease	D/DR3	56	26.3	3.7
Insulin-dependent diabetes	D/DR3	56	28.2	3.3
	D/DR4	75	32.2	6.4
	D/DR2	10	30.5	0.2
Myasthenia gravis	D/DR3	50	28.2	2.5
Sicca syndrome	D/DR3	78	26.3	9.7
Atrophic thyroiditis*	DR3	64	23.8	5.7
Goitrous thyroiditis*	DR5	53	26.3	3.1
Pernicious anemia	Dw5	25	5.8	5.4
Subacute thyroiditis	Bw35	70	14.6	13.7

The relative risk indicates how many times more freqently the disease develops in individuals carrying the HLA antigen in question as compared to the frequency of the disease in individuals lacking the antigen. The data refer exclusively to Caucasoids. Reproduced with permission from Svejgaard et al.[9]

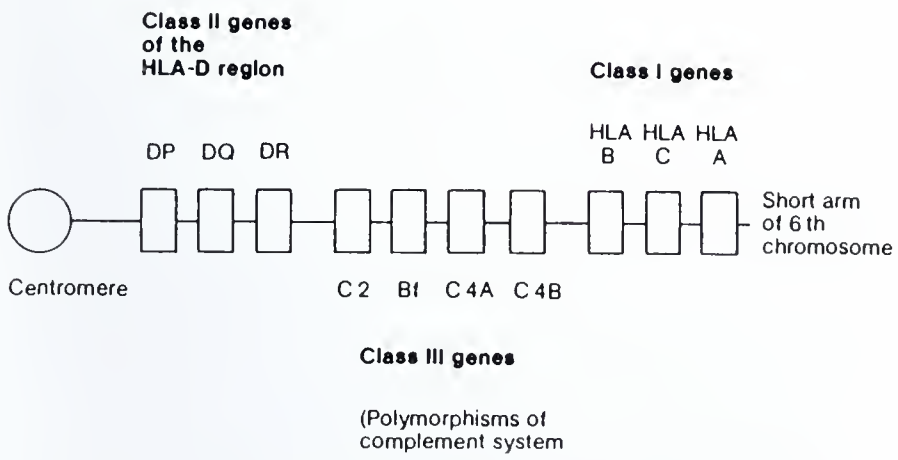


Figure 1. HLA (human leukocyte antigen) region genes (Reproduced with permission from Batchelor)

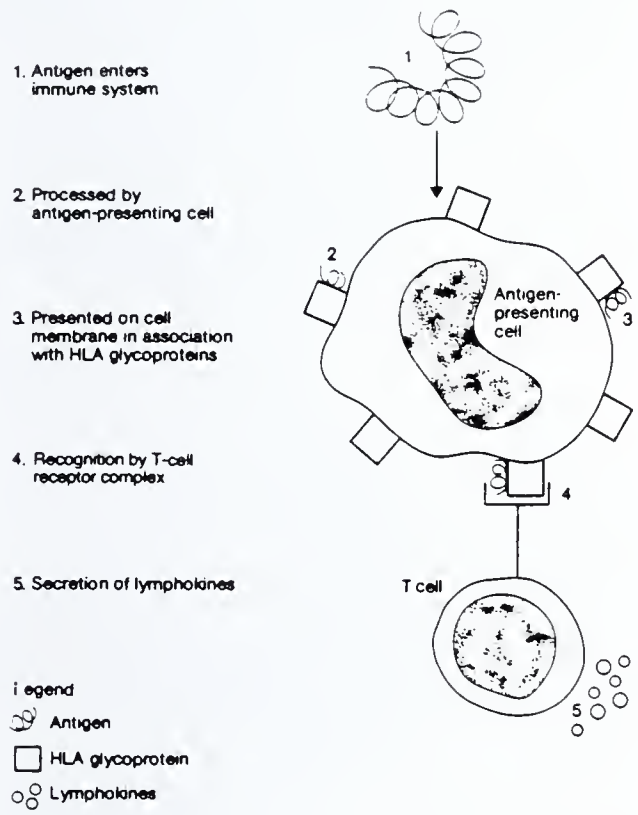


Figure 2. HLA (human leukocyte antigen) molecules and antigen presentation to T lymphocytes (Reproduced with permission from Batchelor)

It has been proposed that the HLA-DR (Ia) molecules on the cell surface of antigen-presenting cells (necessary for antigens to be presented to the immune system (Fig. 2), also confer properties to the immune system which allow it to react in an appropriate or inappropriate fashion.[11] However, the mechanism of imparting a disorder of immunoregulation has not been completely clarified and there may be several other means by which Ir and/or Is determinants may confer susceptibility to autoimmune disease. Bottazzo et al[12] have suggested that in genetically predisposed persons (by virtue of HLA-DR type) synthesis of the DR antigens by the target cells as a result of unknown triggering agents modifying the cell surface of that cell, then leads to the presentation of the target cell antigen directly to immunocytes, thus initiating the immune response. This antigen-centred postulate considers the immune reaction to be a secondary one. However, evidence is now accruing that DR expression on target cells is *secondary* to the initial immune assault, and may act as a potentiating factor, or may have no pathological import, or even by protective against immune injury.[13 16] Antigen presentation is of course a necessary step in immune initiation, but it is likely that the macrophage which expresses DR normally, constitutes the initial antigen presenting cell in autoimmune endocrine disease.

(g) Chemical mediators

T lymphocytes secrete lymphokines which stimulate many other types of cells. Immunoregulatory lymphokines may be divided into two types: antigen-specific, containing components of the antigen binding receptors of T lymphocytes, and non-specific, which do not recognize antigens. The antigen-specific activation of T lymphocytes involves binding, processing and presentation of antigens by the macrophages as mentioned above to T lymphocytes. This process is genetically controlled and limited to the DR (Ia) positive subpopulation of macrophages. The second macrophage-related process capable of activating T lymphocytes is the production of interleukin 1 (IL-1), an antigen non-specific factor synthesized by all macrophages. The main function of IL-1 is to prepare T lymphocytes to respond to antigen and to induce synthesis and secretion of interleukin 2 (IL-2), a T lymphocyte derived mitogenic lymphokine. IL-2 stimulates the proliferation of helper and cytotoxic T lymphocytes and may also induce thymocyte proliferation. IL-2 is involved in the early initiation of the B cell response indirectly through the activation of some form of linked recognition helper function from residual T lymphocytes.[14]

Many other lymphokines are necessary for the immune response, for which space does not permit discussion. These include transfer factor, migration inhibition factor, macrophage activating factor, macrophage chemotoxins, leukocyte inhibitory factor, lymphotoxins, blastogenic factor, and interferons. The latter appear to have immunomodulating properties, can act on B lymphocytes, and can induce DR expression on target cells.[15]

II. Etiology of autoimmune organ specific endocrine diseases

Evidence will be provided below to support the view that each of the organ specific autoimmune diseases is due to a specific abnormality in an antigen-specific clone of suppressor T lymphocytes.[1 2] Each of these defects allows a specific organ-directed "forbidden" clone of autoreactive helper T lymphocytes normally arising at random throughout life, to survive. (In a normal organism the self same "forbidden" clones of autoreactive helper T lymphocytes are also arising, but are immediately suppressed by normal immunoregulatory mechanisms, particularly by specific and non-specific clones of suppressor T lymphocytes).

The random appearance of such spontaneously mutated autoreactive clones of organ-specific helper T lymphocytes in the persons genetically incapable of regulating them, would account for the random appearance of these organ specific diseases in the genetically predisposed persons. In any event, once the specific self-reactive clone of helper T lymphocytes has arisen in this spontaneous and random fashion, it not only survives but also interacts with its complementary antigen on the target cell membrane, and there sets up a localized cell mediated immune reaction, via the intermediate step of antigen presenting cells. This, however, would not require any abnormality in the target

cell membrane, merely the presence and availability of that antigen. However, interferon produced by the helper T lymphocytes could then stimulate DR expression by the target cell,[15] although the pathological importance of this phenomenon is unclear.[16] The clone of autoreactive helper T lymphocytes that has survived in this manner would be amplified and stimulated by the specific antigen, and in consequence would "help" groups of already present, appropriate antigen-specific B lymphocytes which would then produce the appropriate antibody. This rather simplistic schema of course requires many very complex, but non-specific steps involving chemical and cellular events to complete the pathophysiological picture. (Fig. 3)

As mentioned earlier, it appears that the organ specific suppressor T lymphocyte defects are rarely, if ever, complete.[17] However, in some patients with a severe immunoregulatory defect, the mere appearance of the specific autoreactive clone of helper T lymphocytes would be sufficient to initiate a particular disease. In most others, however, the defect is only relative or partial, or even minimal; even after the appearance of the particular autoreactive clone of helper T lymphocytes, there would be partial suppression and the disease would remain occult with adequate (albeit precarious) immunoregulation.[1 2 17] The presence of specific autoantibodies associated with clinical occult disease would be the first and possibly only evidence that immunoregulation was less than complete. However, the particular disease might become overt if some environmental event occurred that further adversely affected the already partially defective and thus precarious immunoregulatory mechanism, by reducing generalized suppressor T lymphocyte function. This explanation may account for the temporal variation in expression of autoantibodies in many of the autoimmune endocrine diseases and in other members of their families.

The recent observation that gamma interferon has produced autoimmune thyroiditis is of interest since this might have occurred via the stimulation of DR on the thyroid cello, ie., unusual antigen presentation.[18 19] This is probably an unusual means of precipitating autoimmune disease; it is almost certain that even in these circumstances, an immunoregulatory disorder would be necessary to permit the autoimmune disease to develop.

III Autoimmune thyroid diseases (AITD)

Autoimmune thyroid diseases (AITD) may be categorized as either Graves' disease (GD), and Hashimoto's thyroiditis (HT) and its variants. This topic has recently been extensively reviewed.[1 2 20 2] (Table 3). The clinical expression of these entities may be markedly different yet there are genetic and pathogenic elements which are similar in, if not comon, to them both; indeed, some workers (although not this author) consider that these two conditions are opposite ends of a spectrum of the same disorder.[1 2] There are, however, elements which differ between these conditions and even between the variants of thyroiditis; these differences will be mentioned below.

While GD is discussed elsewhere in this volume, it may be defined here as hyperthyroidism due to the stimulation of the TSH receptor by an antibody (thyroid stimulating antibody, TSAb), and an appropriate new designation would be "autoimmune thyrotoxicosis".

Table 3

Autoimmune Thyroid Disease

I Autoimmune thyrotoxicosis (Graves' disease, Parry's disease, Basedow's disease)

II Autoimmune thyroiditis

- a) Hashimoto's Thyroiditis
- b) Chronic thyroiditis (fibrous variant)
- c) Lymphocytic thyroiditis of childhood and adolescence
- d) Postpartum thyroiditis
- e) Idiopathic myxedema
- f) Atrophic, asymptomatic thyroiditis

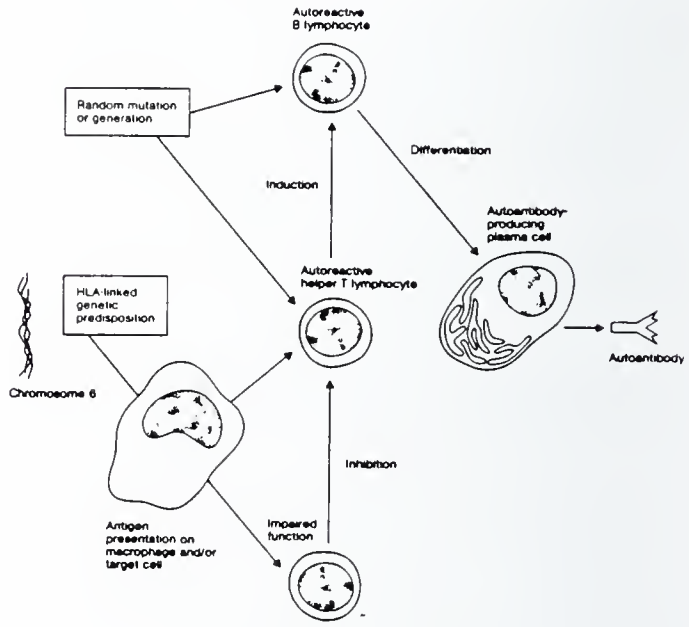


Figure 3. Schema for the hypothesis for each of the organ specific autoimmune endocrine diseases. Human leukocyte antigen (HLA)-linked genetic predisposition appears to result in a specific defect in a clone of suppressor T lymphocytes (specific for each organ specific autoimmune disease). Thus clonal abortion of autoreactive T lymphocytes does not properly occur when the latter arise by normal random mutation. If these autoreactive helper T lymphocytes are not suppressed they will interact with appropriate and specific (already present) B lymphocytes that, in consequence, will produce the appropriate antibodies. (Reproduced from Volpe, R. Triangle 23:95-109, 1984).

Autoimmune thyroiditis was first described by Hashimoto[22] in 1912, who reported four patients with goiter in whom the thyroid histology manifested diffuse lymphocytic infiltration, atrophy of parenchymal cells, fibrosis and an eosinophilic change in some parenchymal cells (Askanazy or Hurthle cells). The variants are noted on Table 3. In the "chronic fibrous" variant, fibrosis predominates and lymphocytic infiltration is less evident. In lymphocytic thyroiditis of childhood and adolescence, fibrosis, Askanazy cells and germinal centres are less obvious than in the adult form, and thyroid autoantibodies tend to be lower in titer or even absent. Postpartum thyroiditis occurs a few months following delivery as a transient form of autoimmune thyroiditis; while in most instances it completely clears, it may sometimes culminate in a chronic form. In idiopathic myxedema, the gland is atrophied rather than hypertrophied. The atrophic asymptomatic form is clinically occult and is often discovered at autopsy. Although there may be subtle genetic and pathogenetic differences between these variants, the pathogenesis is at least similar; the term "autoimmune thyroiditis" thus is now acceptable as a generic term for this group.[2]

There is evidence that HT may have increased in frequency in the last few decades, perhaps owing to increased iodine intake over this time. About 3% of the population have some functional deficiency of the thyroid secondary to autoimmune thyroiditis, whereas up to 16% of elderly females have at least some degree of lymphocytic infiltration within the thyroid gland, although this cannot be recognized clinically.[2] About two thirds of goitres in euthyroid adolescents are due to lymphocytic thyroiditis. GD is also a common disorder, occurring in about 1% of the population.[2]

In both GD and HT there are several aspects which suggest the participation of an autoimmune process (Table 4). The overlap between GD and HT has long been recognized. Indeed, GD and HT frequently aggregate in the same families. There are several reports of identical twins, one with GD and the other with HT. In fact, both GD and HT can cohabit the same thyroid gland; the clinical expression will depend upon which condition predominates. Since there are several genetic, laboratory and clinical elements which are different in these conditions, it is the author's perspective that the two disorders should be considered separate (albeit closely related) entities.

(a) Initial Observations

In 1956, Roitt et al first detected thyroid autoantibodies in the serum of aptients with HT. That same year, Rose and Witebsky[24] described the induction of experimental thyroiditis in rabbits; they mixed one thyroid lobe with Freund's adjuvant (a mixture of killed tubercle bacilli and oil) and reinjected the material into the same animal; thyroiditis developed in the remaining thyroid lobe. Furthermore, during the same year, Adams and Purvis[25] in New Zealand, reported the presence of an abnormal thyroid stimulator in the serum of some patients with GD which was capable of stimulating the guinea pig thyroid gland. This was later termed long acting thyroid stimulator (LATS) and proved to be an IgG. It is now termed long thyroid stimulating antibody (TSAb). These initial observations were the forerunners of an explosion of knowledge which can be only briefly summarized in this section.

(b) Humoral immunity in autoimmune thyroid disease

The various antibodies which may be detected in autoimmune thyroid disease and their possible functions are documented in Table 5 and Fig. 4. TSAb has received most attention because of its unique action in stimulating thyroid cells and ultimate clinical expression as hyperthyroidism. It is now clear that the beta subunit of the TSH receptor is the antigen to which TSAb is the antibody.[2] While there are some workers who maintain that TSAb may not be directed against the TSH receptor itself, most investigators now agree that the evidence for this is convincing.[2]

Originally LATS was assayed by the release of 131-I from primed thyroid glands of guinea pigs after injection of serum from patients with GD; the assay was subsequently modified for mice.[26] Many other assays for the IgGs specific for GD have now been described.[2] The term "thyrotrophin-receptor antibody" should now be used as a generic term for these antibodies since the evidence strongly indicates that the TSH receptor is the related antigen. The term "TSAb" should be employed to refer only to those antibodies which cause stimulation of cAMP in thyroid cells. The radioligand assay which measures binding of the IgG (with inhibition of

Table 4: Immune Stigmata associated with Graves' disease & Hashimoto's thyroiditis

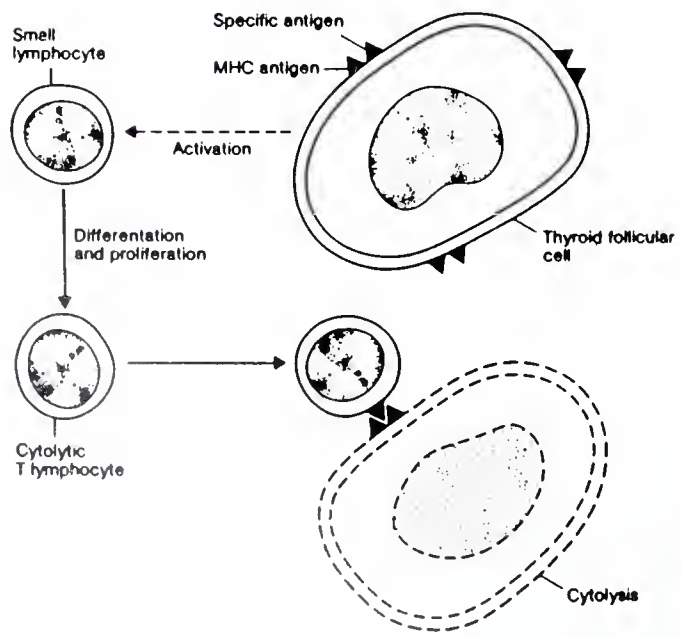
Stigma	Graves' disease	Hashimoto's thyroiditis
Lymphocytic infiltration in thyroid	Frequently present	Almost invariable
Immunoglobulins in thyroid stoma	Yes	Yes
Type of infiltrating lymphocytes in thyroid	B and T lymphocytes, some unidentified lymphocytes	B and T lymphocytes, some unidentified lymphocytes
Immune complexes in circulation	Common	Common
Thymic enlargement	Common	Common
Lymphadenopathy and splenomegaly	Infrequent	---
Relative lymphocytosis	Common	---
Hypergammaglobulinaemia	---	Common
Benefit from corticosteroid therapy	Yes	Yes
Thyroid stimulating antibody	Almost all	Infrequent
Exophthalmos	Common	Occasional
Evidence of cell-mediated immunity	Yes	Yes
Evidence for a defect in suppressor T lymphocytes	Yes	Yes
Other autoimmune diseases in patients	eg. pernicious anaemia, diabetes mellitus, myasthenia gravis, Addison's disease, idiopathic thrombocytopenic purpura, vitiligo	eg. pernicious anaemia, diabetes mellitus myasthenia gravis, Addison's disease, chronic active hepatitis Sjogren's syndrome
Thyroid antibodies in relatives	50%	50%
Thyroid and other autoimmune diseases in relatives	Common	Common
HLA (human leucocyte antibody) genes (Caucasians)	HLA-B8-DR3	Atrophic form: HLA-B8 and HLA-DR3; goitrous form: HLA-DR5
Animal models		Yes

Reproduced by permission by Volpe[2]

Table 5 Antigen-antibody systems involved in humoral responses of thyroid autoimmune disease

Antigen	Antibody (function)	Antibody detection
Thyroglobulin	Thyroglobulin antibody (no clear function)	Precipitin technique; tanned red cell haemagglutination; immunofluorescence on fixed thyroid sections; competitive binding radioimmunoassay; co-precipitation with ^{125}I thyroglobulin; microenzyme-linked immunoassay (ELISA); plaque-forming assay
Microsomal antigen	Microsomal antibody (cytotoxic in conjunction with lymphocytes)	Complement fixation; immunofluorescence on unfixed thyroid sections; cytotoxicity test on cultured thyroid cells; competitive binding radioimmunoassay; tanned red cell haemagglutination; micro-ELISA
Second colloid component	CA_2 antibody (no clear function)	Immunofluorescence on fixed thyroid sections
Cell surface antigen(s)	Membrane antibodies (cytotoxic with lymphocytes)	Immunofluorescence on viable thyroid cells; haemadsorption; binding assays
Thyroxine and triiodothyronine	Thyroid hormone antibodies (bind and prevent hormone action)	Antigen-binding capacity
Antigen not defined	Growth stimulating and growth inhibiting antibodies (may induce or inhibit thyroid growth)	Effects on DNA content per thyroid cell nucleus or G6PD activity per cell
TSH receptor-related antigen	TSH receptor antibodies (may stimulate thyroid cells, inhibit TSH effect, or do both or neither)	Stimulatory assays: (current terms employed for stimulatory assays include human thyroid stimulator, human thyroid stimulating immunoglobulin (TSI), thyroid stimulating antibody (TSAb); Long-acting thyroid stimulator (LATS) bioassay; colloid droplet formation in human thyroid slices; stimulation of human thyroid adenylate cyclase in vitro; cytochemical assay Binding assays: LATS protector assay; inhibition of ^{125}I-thyrotrophin binding to human thyroid membranes (thyrotrophin displacement activity [TDA], TSH binding inhibitor immunoglobulin [TBII]; fat cell membrane radioligand assays; fat cell ELISA

Reproduced with permisssion from Volpe[2]



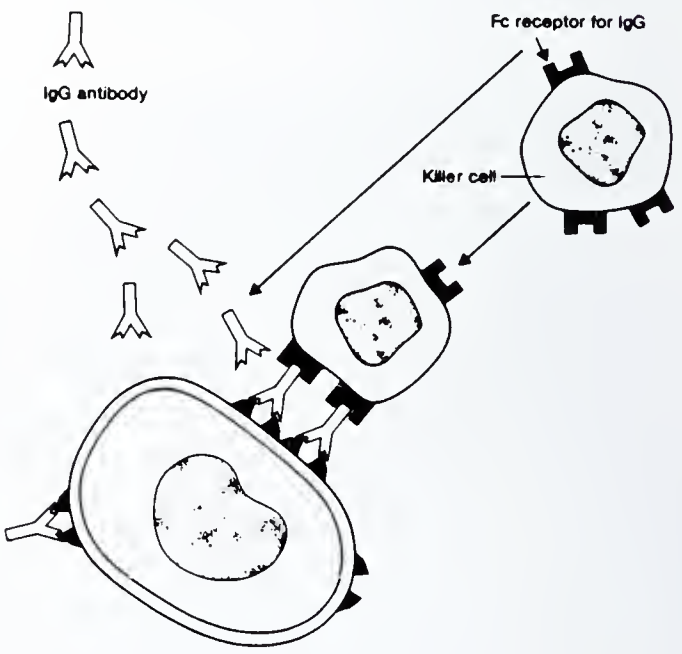
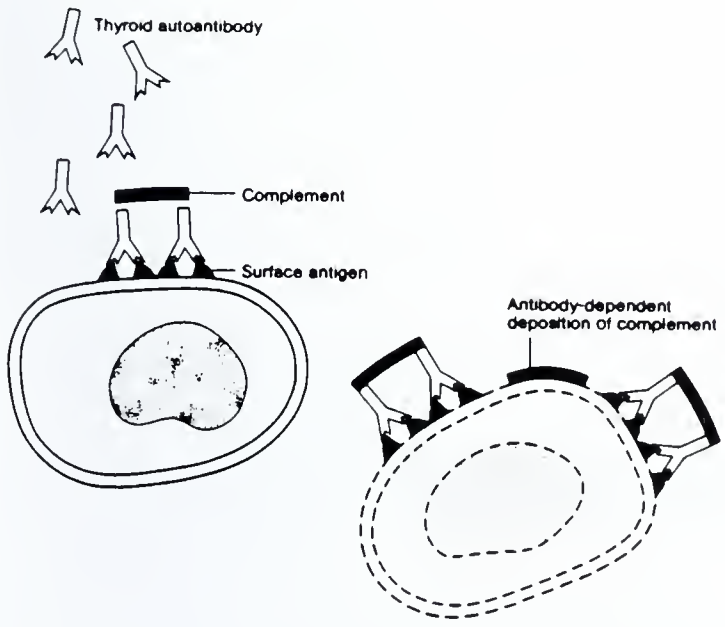


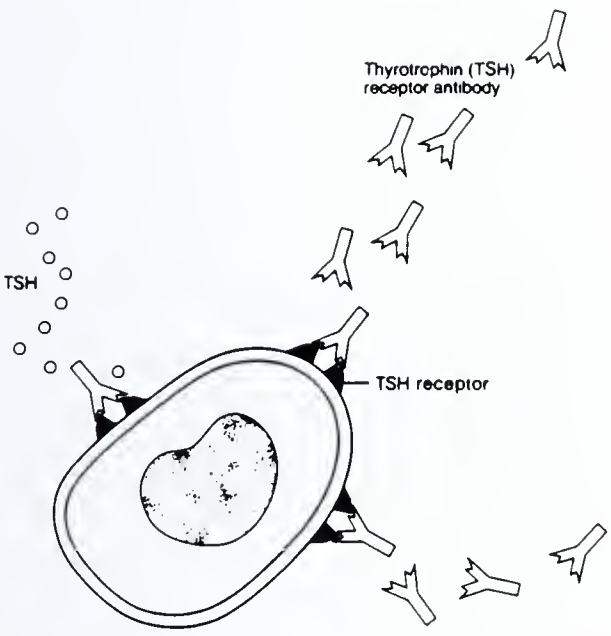
Figure 4. Effects of the autoimmune process on thyroid cells. Mechanisms of thyroid cell damage in autoimmune thyroid disease are depicted in panels A, B and C and effects on growth and function in D, E and F.

(A) Sensitized cytolytic T lymphocytes might interact with specific antigens on the thyroid follicular cells and induce direct T lymphocyte-induced cytolysis.

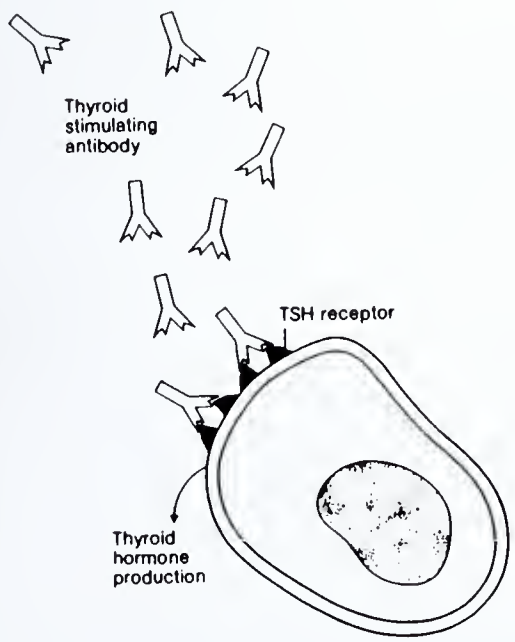
(B) Antibodies against cell membrane aconstitutents can attract "killer" cells (antibody-dependent cellular cytotoxicity ADCC), thus producing cytolysis.



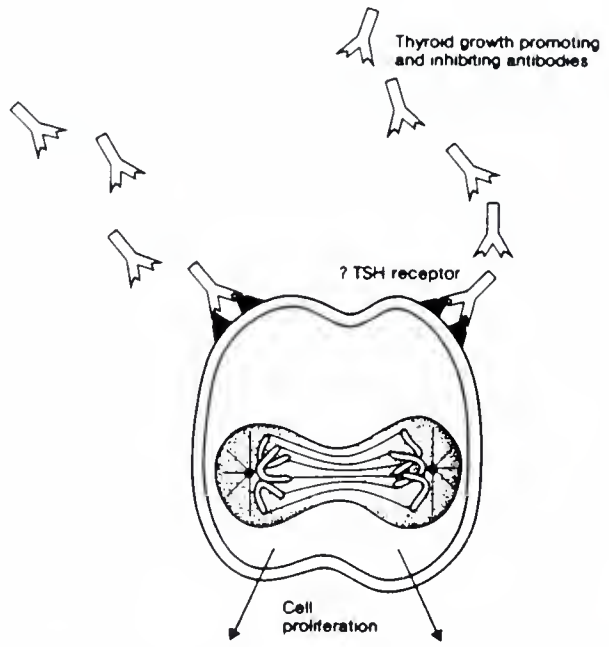
(C) Complement fixing antibody may produce cytolysis more directly by activating complement.



(D) Thyrotrophin receptor antibody may block the access of TSH (thyrotrophin) to its receptors and thus act as a relatively uncommon cause of hypothyroidism.



(E) Graves' disease is most commonly caused by another thyrotrophin receptor antibody (thyroid stimulating antibody) which mimics the action of TSH but is not subject to biological feedback governing the latter hormone.



(F) There is now evidence for a thyroid growth promoting antibody and a thyroid growth inhibiting antibody, although the antigen(s) involved has/have not yet been completely identified.
(Figure 4 is reproduced with permission from Volpe, R. Triangle 23:95-109, 1984.)

binding of labelled TSH) is now generally referred to as "thyrotropin-binding-inhibitory immunoglobulin, TBII". Some IgGs positive in the TBII assay will not stimulate the thyroid cells, and some may even inhibit TSH activity in vitro and in vivo contributing to hypothyroidism.

Using an assay measuring the generation of cAMP in human thyrocytes, several laboratories have recently demonstrated TSAb in about 95% of patients with untreated GD.[2] In those laboratories, the assay is not only sensitive but virtually specific. Another extremely sensitive but difficult cytochemical assay permitted detection of a stimulating factor in the serum of all patients with GD who were studied. These results were considered inconclusive since this factor was also detected in most patients with toxic multinodular goitre and even with euthyroid goitre. TSAb in pregnant patients crosses the placenta and when present in high titer, may cause neonatal passive transfer GD. In adition, TSAb tends to decline in many patients with long term antithyroid drug therapy; conversely the continued presence of TSAb is associated with a high relapse rate following discontinuance of such therapy.

Other thyroid antibodies will be only briefly mentioned in this section although reference is made to them in Table 5. The antibodies that are most important clinically are thyroglobulin and thyroid microsomal antibodies. A high titer of thyroglobulin antibody, a non-complement fixing antibody is found in about 55% of patients with HT and 25% of patients with GD. It occurs less often in patients with thyroid carcinoma and other (nonthyroidal) autoimmune disorders, and low titers are found in 10-15% of normal subjects (particularly elderly women). Thyroid microsomal antibody is a complement-fixing antibody that is found much more frequently in autoimmune thyroid disease when compared to antithyroglobuliln. It is observed in about 95% of patients with HT, 90% of patients idiopathic myxedema and 80% of patients with GD when studied with the hemagglutination technique. It correlates much more closely with histological lesions in HT when compared to

thyroglobulin antibody and also has a closer relationship with evidence of thyroid dysfunction, since about 72% of those with persistent microsomal antibodies will be shown to have thyroid dysfunction.[2] Antibodies to the thyroid hormones themselves are only of clinical importance when the thyroid gland is incapable of responding to excess TSH. In such instances, antibodies to T4 and T3 will result in a reduction in the free moiety; the addition of exogenous thyroid hormone may not result in the expected clinical improvement until extremely high dosages have been reached. Antinuclear antibodies are also found in autoimmune thyroid disease, as are antibodies to cell membranes and antibodies to a colloid component other than thyroglobulin. Antibodies which induce growth of thyroid cells or conversely inhibit growth, have been found in various types of thyroid disease, although their precise nature has yet to be clarified.[2]

Autoantibodies to a few other organs such as gastric antigens, islet cells, etc. are found more commonly in patients with autoimmune thyroid disease by virtue of the inheritance of more than one disease susceptibility gene lying in close proximity on chromosome.[6]

(c) The T lymphocytes autoimmune thyroid disease.

Studies of T lymphocytes and numbers and function (cell mediated immunity) have been two pronged, i.e. those of generalized (non-specific) suppressor T lymphocytes and, conversely studies of antigen-specific suppressor T lymphocyte function.[1 2 17 27] In general, there appears to be a reduction in the number and function of generalized suppressor T lymphocytes in the hyperthyroid phase of GD and these tend to normalize as thyroid function itself improves. This will occur whatever the form of therapy, including 131-I, and does so whether or not TSAb remains strongly positive. With some exceptions, results have usually been reported to be normal in euthyroid HT.

The observation that there is also a reduction in suppressor T lymphocytes in toxic nodular goitre[28], but that it is less marked than in GD suggests that hyperthyroidism has to be severe and perhaps prolonged to have such an effect. Indeed, recent evidence from our own laboratory indicates that this is the case.[29] Thus, the reduction in generalized suppressor T lymphocytes does not appear to be a primary pathogenetic factor. However, by its additive effect, superimposed on the antigen-specific suppressor T lymphocyte defect to be noted below, this secondary effect of hyperthyroidism on the immune system may act as a self perpetuating mechanism in the disease. (Moreover, environmental factors such as stress, infection, drugs or againg, may have similar adverse effects on generalized suppressor T lymphocyte function, and thus may precipitate the disease by a similar additive effect.)[1 2 30]

Conversely, studies of antigen-specific suppressor T lymphocytes function have yielded results different in quality than those described above.[2 17 27] Firstly the idea that there could be an antigen-specific disorder in suppressor T lymphocytes seems more rational than that of a generalized disturbance in suppressor T lymphocyte function; the latter would result in multiple clinical disorders of immunoregulation, and thus would not accord with genetic observations in which autoimmune thyroid disease appears much more commonly in families where the propositus also has autoimmune thyroid disease rather than other autoimmune disorders. There are now several reported studies indicating the presence of an organ specific defect in suppressor T lymphocyte function in autoimmune thyroid disease, in which the observation does not relate to the thyroid function of the patient (i.e. whether that patient is hyperthyroid, euthyroid or hypothyroid).[31,41] While one group has not been able to confirm some of these findings,[42] the weight of evidence now supports this thesis rather strongly. It appears that the organ specific defect in suppressor T lymphocytes is usually a relative one,[38 41] and may relate to a reduction of organ-specific H2-receptor bearing suppressor T lymphocytes.[32 38]

(d) The role of the antigen

There is no evidence for an alteration in the thyroid antigen.[2] AITD appears to be primarily a disorder of immunoregulation with the organ dysfunction resulting from an antigen-specific attack mounted by inadequately suppressed lymphocytes directed toward these specific cellular targets. Certainly the antigen has to be present and presented to the specific cells in a specific fashion for this attack to be mounted. This requires expression of HLA-DR antigens on the antigen presenting cell; while this has generally been considered to be the macrophage primarily, the thyroid cells can also express DR and act as antigen presenting cells.[12] However, evidence developed in our own laboratory[13] and elsewhere[17] has shown that DR expression by thyroid cells is a secondary event, and that lymphocytes and macrophages are necessary for the thyroid cells to express DR in this fashion. Thus, this author does not agree with Bottazzo et al[12] that the thyroid cell by expressing DR on its cell surface because of some prior stimulus, acts as a precipitating element in the induction of autoimmune thyroiud disease. (It is, of course, possible under unusual circumstances that this might happen, but it is very unlikely to be the usual means of autoimmune induction). In the view of the author, therefore, the step of presentation of the antigen (while important) is not seen as a primary event, but is secondary to the immune disturbance. Moreover the suggestion that the primary event is a viral infection[12 43] is entirely speculative and for which there is no evidence; the initiation of the immune assault may well occur via variations in immunoregulation, as discussed above.

(e) Genetic control of the immune response.

While the association of histocompatibility genes has been described earlier in this section, a few points may be made about the relationship of such studies to autoimmune thyroid disease.[2 8] In mice, genes that map in the region that corresponds to the HLA-D locus in humans are responsible for controlling the response of helper or suppressor T lymphocytes to a given antigen. In humans, GD has been found to be associated with HLA-DR3 (Caucasians), while goitrous HT has been associated with HLA-DR5, and atrophic thyroiditis, with HLA-DR3. Previous observations that linked GD with HLA-B8 probably reflected a linkage disequilibrium between HLA DR3 and B8. However, only about 58% of patients with GD were found to have HLA

DR3; the level in the general population is about 20%. Moreover, the possession of HLA-DR3 does not predict certain GD during a particular person's lifetime. Indeed, the relative risk increases only six fold if one has this particular gene. Thus, only about 6% of these who have this gene will actually develop GD. Conversely about 42% of those who do develop GD do not possess the gene. It is therefore clear that the disease susceptibility gene for GD is not HLA-DR3 but may be in close proximity in linkage disequilibrium. How this genotype may cause an abnormality in a specific clone of suppressor T lymphocytes is unknown, as is the molecular nature of the abnormality.[8-11] It has been suggested that the mechanism will operate via the presentation of the antigen to the lymphocyte but even this point remains to be clarified.

(f) Nature of the remission of Grave's disease

More than one form of clinical remission occurs in GD.[2] Surgical or 131-I destruction of sufficient tissue may prevent recurrence. Conversely continuous *spontaneous* thyroid damage (probably immunologic) may bring about clinical remission. Another important form of remission is one in which all immunological stigmata of the disease disappear including thyroid autoantibodies, TSAb and evidence of sensitization of T lymphocytes.[44] This form of remission may occur only in those patients with a partial defect in immunoregulation; in these patients an occult specific suppressor T lymphocyte abnormality is rendered overt and hyperthyroidism initiated, by effects on generalized suppressor cell function by such mechanisms as stress, infection, aging and drugs (as suggested above). This is therefore reversible when that circumstance is overcome. The restoration of a euthyroid state by whatever means (antithyroid drugs, 131-I, or surgery) should further relieve the situation, since the effects of hyperthyroidism per se on the immune system (see above) would be reversed under these circumstances. In addition, social factors, rest, the passage of time, the clearing of infection, the use of sedation and other non-specific measures will each serve to allow the partially defective immunoregulatory system to be restored to its previous functional capacity.[5 17]

Those persons with a presumed severe defect would not be expected to enter an immunological remission no matter how long their antithyroid drugs (ATD) were continued or what the form of therapy was employed. Only those remissions associated with spontaneous or iatrogenic thyroid destruction would occur in this group. There is some evidence for a genetic basis for the ability to remit or relapse, also consistent with the hypothesis for remission as described above. It has been reported that patients manifesting HLA-DR3 tend to relapse more frequently after ATD therapy when compared with those who lack the HLA gene, although this has been disputed.[2] Moreover those who are still positive for TSAb at the end of the treatment period with ATD will also almost always relapse.

(g) Implications for therapy in Graves' disease

Our understanding of the immune nature of GD has so far led to few changes in the philosophy of its management. Since there is, however, evidence that it may be possible to predict which patient will remit after ATD therapy, some selection has been initiated of patients who should be on long term ATD therapy versus those who should have ablative therapy. There is also evidence that ATD are themselves immunosuppressive; it has been claimed that it is via this mechanism that the remissions occur.[20 45 46] It is, however, difficult to reconcile this proposal with the fact that many patients continue with immunological activity throughout the course of the treatment, no matter what dosage of ATD is employed, and no matter how well the hyperthyroidism is controlled. It is also difficult to comprehend how a long term remission after cessation of therapy would persist in view of the short duration of action of the drug. Moreover, as we have seen above, normalization of thyroid function is attended by a return to normal of the suppressor/helper T lymphocyte ratio. For these and other reasons it seems more likely that the normalizing effect of the antithyroid drugs on thyroid functionis more decisive in bringing about the remission, rather than their immunosuppressive effects.[5]

Using 131-I therapy de novo is also associated with immunological perturbations, namely a transient rise in TSAb and other thyroid autoantibodies, followed by an ultimate decline.[2] This may be due to liberation of thyroid antigen affecting the already disturbed immune system or an effect of the irradiation on suppressor T lymphocytes. Since radioactive iodine has been noted to cause an increase in exophthalmos in 5-10% of patients,[47] perhaps by the continued adverse effect of hyperthyroidism on the immune system, or perhaps because of the above 131-I perturbation of the immune system, the author prefers to use ATD for at least a few months until a euthyroid state has been achieved even in those patients who are destined to have 131-I thereafter. This approach is speculative in the hope that it may cause a reduction in exophthalmos. A study is currently being conducted to try to resolve this point.

Finally, subtotal thyroidectomy is often associated with a decline in TSAb activity, perhaps because most of the offending thyroid-committed lymphocytes are removed with the gland.[2] Recurrences following surgery would have to be associated with (a) sufficient remaining thyroid parenchyma to respond to TSAb and (b) sufficient remaining thyroid committed lymphocytes to mount the immune attack.

(h) The pathogenesis of ophthalmopathy

The ophthalmopathy of GD is still of unknown etiology.[1 2 20 21 47-49] It may precede, accompany or follow hyperthyroidism and the vast majority of patients (but not all) with exophthalmos will manifest hyperthyroidism sooner or later. However, about 5% of patients with definite "euthyroid Graves' ophthalmopathy" have no such past or present history of hyperthyroidism. Moreover, ophthalmopathy has been associated with Hashimoto's thyroiditis and with primary hypothyroidism. While in many patients with "euthyroid ophthalmic Graves' disease" who show no clinical evidence of thyroid disease, there may be some occult abnormality or thyroid antibodies, there remains a small group with no laboratory evidence of thyroid disease whatsoever.

Conversely, even minimal ocular disease, as judged by ultrasonography or measurement of elevated intra-ocular pressure, on upward gaze, is quite common in patients with GD who do not manifest *clinical* eye signs. Nevertheless, there remains a residual group of Graves' patients with no ocular abnormalities whatever.[47 49]

Recent studies of antibodies against eye muscles have begun to illuminate the relationship between exophthalmos and the hyperthyroidism of GD. Antibodies to the eye muscles are generally positive in patients with oculopathy but negative in patients with Graves' hyperthyroidism without eye disease.[49] These studies suggested exophthalmos and hyperthyroidism are two separate entities (no matter how closely related they are genetically and pathogenetically). We had proposed over a decade ago that Graves' ophthalmopathy should be considered an organ specific autoimmune disease separate from that of the hyperthyroidism or GD but very closely linked to it.[1 2] Space does not permit a discussion of other theories for exophthalmos for which the reader will have to be referred elsewhere. It may be suggested that the gene that causes hyperthyroidism of GD is in extremely close proximity to that for exophthalmos allowing for a considerable overlap. Moreover, the hyperthyroidism per se may exert an adverse effect on generalized suppressor T lymphocyte function, as mentioned above, thus tending to precipitate other associated autoimmune diseases which may be previously occult, perhaps accounting for the frequency of the simultaneous appearance of exophthalmos with the hyperthyroidism. It must, however, be conceded that this view is not universally held.

IV The immunology of diabetes mellitus

It is now increasingly evident that Type I (insulin dependent) diabetes mellitus (IDDM) is an autoimmune process. This brief account will only serve to summarize the evidence which stands behind the above statement and the reader is referred elsewhere for more detailed discussion.[1 2 50-52]

(a) Genetics

It is evident that IDDM tends to aggregate in certain families and thus is genetically induced. The concordance rate in identical twins is in the order of 50%; the disparity of the age of onset in the IDDM twins indicates that the disease seems to occur at random in those predisposed to develop the disease.[1 2 50-52] This implies that there is, firstly a genetic factor, and secondly a non-genetic factor which has vexed the imagination of many observers. It has led to the search for environmental factors in the development of this disease, such as viruses and drugs. Viruses particulary have long been proposed as etiological agents in IDDM and the various reviews cited above will provide the background evidence for this proposal. What was considered to be the most compelling evidence that IDDM in man could be caused by a virus was the finding of a Coxsackie B4 virus which had been isolated from the pancreas of a child who had died with diabetic ketoacidosis and overwhelming viral infection.[53] However, a more recent pathological examination of the Islets of Langerhans of this child demonstrated evidence of previous chronic beta cell damage that *preceded* the acute viral infection.[54]

While therefore there are experimental models which indicate that viruses may induce diabetes mellitus in vulnerable animals by infecting the islets, the evidence is certainly not compelling in humans.[1 2 50 52] However, it is of considerable interest that approximately 20% of children with congenital rubella will develop diabetes mellitus in later life.[50-53] This diabetes is somewhat atypical in that it is often non-insulin dependent, although it does occur usually in patients who are HLA-DR3 and/or DR4 positive and many of these express islet cell antibodies. In these cases, the diabetes does not occur at the time of the infection but years later, and the same children have a high incidence of thyroid autoantibodies. It is thus altogether likely that this is not a result of viral-induced target cell damage but due to an effect of viruses on the immune system in genetically predisposed individuals.

The genetic predisposition relates to genes in the region of the HLA-DR alleles residing on chromosome [6]. Type 1 diabetes is associated with the HLA alleles DR3 and DR4.[8 9 11 50-52] Approximately 95% of persons with IDDM are positive for these alleles as opposed to 40% of normal persons. Moreover, where siblings are identical for the HLA genes, the risk of diabetes is increased 90-fold, while a sibling having only one of the HLA loci in common with the diabetic sibling possesses a 37-fold increased risk.[50 52] On the other hand, an HLA non-identical sibling has a risk for IDDM similar to that of the general population. As with autoimmune thyroid disease, however, it should be emphasized that the presence of these genes does not ensure the development of IDDM, as 40% of the Caucasian population have these self-same genes and only a very small proportion of those will develop diabetes unless they happen to be members of families in which diabetes is present already. Moreover, one can have patients with IDDM who have neither DR3 nor DR4 alleles. It is thus felt that the diabetogenic genes reside close to the above genes and are in linkage disequilibrium with them. This is also the case for many other organ specific autoimmune endocrinopathies. Indeed, patients with IDDM will often be found to have autoantibodies to other organs and there is also an increased incidence of certain other organ specific autoimmune diseases, generally related to HLA-DR3 alleles, most commonly autoimmune thyroid disease.

(b) Immune phenomena

It is now evident that in most patients with IDDM, islet cell antibodies precede overt diabetes, sometimes by many years, and even measurable endocrine disturbances may proceed the overt expression of the disease.[50-52] A variety of anti-islet cell antibodies have now been described in IDDM and several methods for detecting these antibodies have been reported.(Table 6) The cytoplasmic immunofluorescent antibody assay using unfixed pancreatic tissue is considered the most specific of such antibody assays available. Several groups have now reported that up to 80% of patients have anticytoplasmic antibodies at the time of onset of the disease. However, some relatives of patients who have developed such antibodies have not gone on to

Table 6: Anti-islet antibody assays

1. Anti-"cytoplasmic" anti-islet antibodies
   a. frozen sections of normal human pancreas
   b. sections of Bouin's fixed pancreas

2. Anti-surface islet cell antibodies
   a. 51Cr release rat islet cells
   b. 51Cr release RINm5F cells
   c. ethidium bromide uptake rat islet cells
   d. indirect immunofluorescence on living islet cells
   e. 125I-protein A radioassay
   f. beta cell specific surface assays

3. Immunoprecipitation
   a. 64K protein
   b. insulin

Reproduced with permission from Eisenbarth[50].

develop overt diabetes.[54] Conversely, not all patients who develop overt IDDM are positive for these antibodies.[55 56] It has been suggested that the islet cell antibodies are markers of ongoing beta cell destruction, but it is unlikely that they are pathogenic themselves. Threre really is no evidence that the antibodies can induce islet cell damage and it is much more likely that cytotoxic T lymphocytes, in conjunction with macrophages induce the cell damage directly.[57]

While the precise antigen has yet to be completely settled, Baekkescov et al have now immunoprecipitated a 6400 Dalton islet cell protein with the sera of patients with Type I diabetes. It has been clearly demonstrated that in the acute active phase of IDDM there is an increase in activated T lymphocytes expressing the DR (Ia) antigen. (Fig. 5) [50-52 59] Indeed, Bottazzo and his colleagues[59] have shown evidence that there is aberrant expression of DR antigens on the cell surface of some beta cells in diabetic patients and has proposed that this is the initial step triggering the autoimmune process in appropriate vulnerable persons. (However, there is now increasing evidence that DR expression on target cells is secondary to the immune assault itself, is thus an intermediate step and is not a primary precipitant).[13 17]

In vitro studies of T lymphocytes have been of interest. Nerup et al60 in 1971 reported that migration of lymphocytes from IDDM patients was inhibited by preparations of mammalian islets. This has been confirmed recently by Topliss et al[34] using human islet cell tissue. In 1976 Huang and Maclaren, using lymphocytes from IDDM patients, showed evidence of lymphocyte mediated cytotoxicity against an insulinoma cell line. In 1981 Boitard et al[61] demonstrated that lymphocytes from IDDM patients inhibited insulin release by isolated mouse islets.

(c) Evidence for an organ specific defect in immunosuppression

Fairchild et al[62] in 1980 studied non-specific and specific suppressor cell function in IDDM. Antigen specific suppressor cell function was evaluated by suppressor cell activation with 100 gs of guinea pig islet cell homogenate (experimental culture) or splenic cell homogenate (control

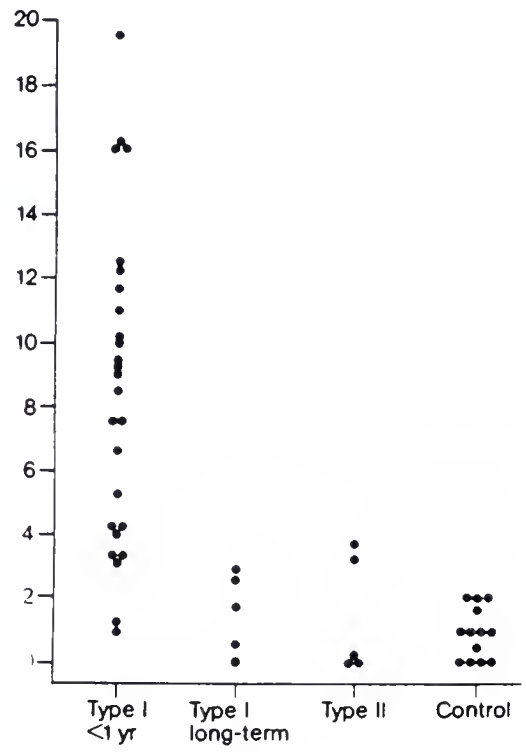


Figure 5. Percentage of HLA-DR (Ia) positive T lymphocytes in insulin dependent diabetes mellitus. Please note the very high values occurring immediately following diagnosis, gradually falling to control levels after long term management. Similar findings have been noted in Graves' disease. (Reproduced with permission from Eisenbarth 50)

culture) for 24 hours. Experimental and control cultures were washed and co-cultured with fresh cells stimulated with islet cell homogenate. Co-culture cell proliferation rates were measured by tritiated thymidine incorporation. These authors demonstrated that specific suppressor cell activity was lower than in the control population.

Topliss et al[34] have mixed T lymphocytes from patients with IDDM with the T lymphocytes from patients with Graves' disease, observing the response to human thyroid antigen on the one hand and to human islet cell antigen on the other, using the migration inhibition factor test. The lymphocytes from the IDDM patients alone produced MIF in response to islet cell antigen but this was abrogated when Graves' disease T lymphocytes (positive alone in the MIF system against thyroid antigen but negative against islet cell antigen) were added. Thus the Graves' disease lymphocytes acted as "normal" T lymphocytes in the system in which the diabetic T lymphocytes were incubated with islet cell antigen. T lymphocytes from normal persons but *not* lymphocytes from other patients with IDDM, would also abrogate MIF production when added to the IDDM T lymphocytes in response to the islet cell antigen. This is evidence that there is an organ specific defect in suppressor T lymphocyte function in IDDM and that it is separate from that of Graves' disease. Lohmann et al[63] have also shown that the cytotoxic effect of lymphocytes from newly diagnosed Type I diabetics on isolated rat islets could be abolished by the addition of lymphocytes from healthy persons, but not by lymphocytes from other diabetic patients. This evidence is also in accord with the notion that there is an organ specific defect in suppressor T lymphocyte function in IDDM; the latter study should however be repeated using lymphocytes from patients with other specific autoimmune diseases to establish the specificity of the findings.

The idea that there is an organ specific defect in suppressor T lymphocyte function in IDDM has not yet become popular amongst investigators in this field. However, the evidence is beginning to accrue that there is indeed such a disturbance which may be the genetic factor which has been the elusive missing link in the pathogenesis of this disease.

(d) Generalized suppressor T lymphocyte function

There are several reports indicating that there is a reduction in generalized suppressor T lymphocyte function or numbers in the early phases of diabetes mellitus but this appears to clear as the disease becomes stable.[50 52] This may be analagous to the situation in severe hyperthyroidism where there also are similar findings. It may be conjectured, however, that such generalized reductions in suppressor T cell functionor numbers may represent a consequence of some preceding stress, or may be secondary to the stress of the metabolic disease itself. This may prove to be an important factor as it may be additive and superimposed on the organ specific defect, and thus may act as a precipitant or a perpetuating factor until the particular cause or causes of the generalized disturbance are brought under control (e.g. by control of the disease). This author would therefore speculate that one does not require any triggering mechanism affecting the target cell directly to precipitate the disease. There is no evidence tha the target cell itself is abnormal prior to the immune assault, and it may be a passive captive to the immune events. While it is possible that perturbation of the antigen could be an (unusual) precipitating factor, all that one really requires is perturbation of the immune system leading to insufficient control by islet directed helper T lymphocytes. This could readily come about by a combination of a relative organ specific defect in suppressor T lymphocytes, plus the addition of any generalized disturbance in suppressor T lymphocytes resulting from variable environmental factors, such as viral diseases, stress, trauma, etc. (see Autoimmune Thyroid Disease above for fuller discussion.) There is thus no need to invoke an antigenic disturbance in this theory.

This would be in accord with the recent observation by Sutherland et al[64] who transplanted pancreatic segments from three normal monozygotic twins (more than 15 years discordant) to their diabetic twin-mates. No immunosuppression therapy was provided since the recipients were monozygotic twins. At first the diabetic state cleared, but within four months specific beta cell lymphocytic infiltration and destruction occurred, despite the passage of 15 years. Thus, without any apparent antigenic stimulation other than the presence of the normal islets, the immune system was still abnormal and capable of re-enacting the disease. This would seem to be most compatible with the views regarding pathogenesis as proposed above.

(e) Immunotherapy

It is of interest that a fourth twin in the above study who has also been transplanted with a pancreatic segment was treated prophylactically with Azothioprine following the transplantation and the diabetic state did not recur at the time of writing.[64] This raises the issue of immunotherapy in the treatment of IDDM before total destruction of the beta cells has occurred. Since beta cell destruction does occur at a subclinical level for years prior to the onset of overt diabetes, it would clearly be of importance to predict which person is going to develop diabetes and to commence treatment before complete destruction of the beta cells has occurred. This should be possible, using islet cell antibodies when they are made more readily available with perhaps newer and somewhat easier techniques. Perhaps the most important study in this respect has been performed by Dupre, Stiller et al[65] using Cyclosporine. Patients have been started on this therapy at the time of original diagnosis despite the fact that considerable beta cell loss has already occurred. Approximately one half of the patients nevertheless, have gone into a prolonged remission with this therapy. Because of its side effects, it is not clear whether this therapy will stand the test of time, but it is a most interesting and encouraging new development. Moreover, Harrison[66] has recently been studying the use of Azothioprin in similarly selected diabetic patients immediately after diagnosis and has shown a similar reduction in insulin requirement.

(f) Experimental and animal models.

Approximately 60% of a non-obese, outbred colony of biobreeding Worcester (BB/W) rats develop diabetes within 60-120 days after birth.[51] This is a genetic disorder, with at least two genes contributing to the development of the disease. One gene is expressed in an autosomal recessive fashion with 100% penetrance and leads to a severe T cell lymphopenia. Another gene is linked to the histocompatibility region. No environmental factor has been implicated in the development of the disease; it comprises an extremely useful model for investigation of the pathogenesis and treatment of the human disorder, although caution must always be exercised about the completeness of the analogy.

V Autoimmune Diseases of Adrenals, Gonads, Pituitary and Parathyroids: Autoimmune Polyendocrine Disease

A) Addison's Disease

The orginal description by Addison[67] in 1855 of eleven examples of this disorder include cases now recognizable as idiopathic adrenal atrophy, as well as tuberculosis of the adrenal gland and metastatic carcinoma. While tuberculosis once accounted for the majority of this condition, in recent decades idiopathic atrophy (autoimmune adrenalitis) has become the most common form of the condition in Western countries.

There is now ample evidence that idiopathic Addison's disease is almost always due to autoimmune adrenal destruction.[1 2] The evidence derives from the histology of the disorder, the finding of autoantibodies against the adrenal cortex in many patients with this condition, the association with other organ specific autoimmune diseases, studies of HLA antigens, the genetics of Addison's disease, and experimental observations.[1 2]

Autoimmune adrenalitis has been produced in experimental animals by means of immunization with adrenal homogenates and adjuvants. Moreover, the passage of lymph node cells from rats with experimental autoimmune adrenalitis to normal recipients has produced adrenalitis in the passively transferred recipients. Success in producing this form of adrenalitis depends on the genetic background of the immunized animals.

In the human disease, both adrenal glands are found to be exceedingly small and difficult to locate at autopsy. The capsule is generally thickened and the cortex is usually completely destroyed. The remaining adrenocortical cells may be single or in small clusters. A mononuclear cell infiltration is invariable with lymphocytes, plasma cells, macrophages and occasionally germinal centres. The few remaining parenchymal cells are surrounded by the heaviest infiltration of lymphocytes and variable amount of fibrosis is evident.[1 2]

(a) Humoral immunity

Anti-adrenal antibodies are detectable in about two thirds of patients with autoimmune Addison's disease.[1 2] The means of detection have included the complement fixation test, or immunofluorescence. They tend to be more common in those patients with short duration of disease, and in those who develop the disorder at an early age. The titers of adrenal autoantibodies tend to be lower than those for thyroid or gastric antibodies in autoimmune thyroid disease or pernicious anemia respectively, but may persist for many years following adequate medical therapy. Such antibodies are found very rarely in the control population and are also quite rare in first degree relatives of patients with Addison's disease (providing that these relatives do not have idiopathic hypoparathyroidism). In idiopathic hypoparathyroidism, adrenal antibodies occur quite frequently in 25-30% of patients.

In patients with Addison's disease who have anti-adrenal antibodies, there may also be antibodies which react with ovary, testis, and steroid-producing cells in the placenta. This cross-reacting antibody may be associated with primary ovarian failure. Although these are IgG antibodies and thus cross the placenta, there is no evidence that they are able to cause damage to the fetal adrenal.

In patients with autoimmune Addison's disease there is a very high incidence of antibodies to other organ antigens, including not only steroid producing cells, but parathyroid, thyroid, islet cell antigens or gastric antigens. There is also a much higher incidence of overt autoimmune diseases associated with these same antibodies (Table 7). Thus, in patients with autoimmune Addison's disease, careful consideration should be given to the probability that there will be other organ specific autoimmune diseases either in an overt or an occult (serological) form.[71 72]

(b) Genetic studies

Autoimmune Addison's disease aggregates in families and tends to be familial. It is generally considered to be an autosomal recessive characteristic although the inheritance has not been completely settled. There is an increased incidence of HLA-B8 and DR3 in Caucasians with autoimmune Addison's disease similar to that seen with Graves' disease. This is only true, however, with patients who do *not* have hypoparathyroidism and generalized candidiasis (see autoimmune polyendocrine disease below).

(B) Ovarian failure

About 25% of women with idiopathic Addison's disease will be found to have premature menopause or amenorrhea.[1 2] The majority of these have circulating antibodies against steroid-secreting cells in their serum. Such antibodies are almost never detectable in patients with amenorrhea *not* associated with Addison's disease. The question arises as to whether autoimmune ovarian or testicular failure is closely associated, but separate organ specific autoimmune disease, or whether it results from cross-reactivity by antibodies primarily reacting against adrenal constituents. The evidence would suggest that steroid cell antibodies are not organ specific but cross-reactive, with specific antigens shared between the adrenal cortex and some steroid producing cells in the gonads and placenta. This would then explain the finding of antibodies against ovarian constituents in some male patients with autoimmune adrenal failure. There is also some evidence that the cross-reactivity also occurs with sensitized T lymphocytes just as much as with the autoantibodies which may be cross-reactive. There may be a few instances in which premature menopause secondary to autoimmune process may not be related to Addison's disease, but this circumstance is rare.

Histological features of the ovaries of patients with amenorrhea associated with autoimmune Addison's disease will show lymphocytic infiltration and fibrous tissue, similar to that seen in thyroid autoimmune disease. Autoimmune tes-

Table 7. Associated organ-specific auto-immune diseases in patients with auto-immune adrenalitis (Addison's disease)

Associated disorders	Middlesex Hospital series		Edinburgh series	
	No	%	No	%
Primary ovarian failure	25	8	51	18
Thyroid disease	(56)	(19)	(46)	(16)
Primary thyrotoxicosis	20	7	21	7
Primary myxoedema	33	11	20	7
Goitrous AI thyroiditis	3	1	5	2
Insulin-dependent diabetes	45	15	27	9
Idiopathic parathyroid deficiency	12	4	16	5.5
Pernicious anaemia	7	2	12	4
Positive prolactin-cell antibodies (?subclinical hypophysitis)	(12)	(4)	-[b]	-[b]
Number of patients affected	118[a]	40	106	37
Total number of patients	294		289	

[a] Discrepancy in numbers due to polyendocrine cases
[b] Not tested

Reproduced with permission from Doniach and Bottazzo (Middlesex series), Clinical Immunology Update, ed. Franklin, E.C., Elsevier/North Holland, New York, 1981, pp.96-109; and Irvine (Edinburgh series), In: Advanced Medicine, ed. Besser, G.M., Pitman, Tunbridge Wells, Vol. 13, 1977, pp.115-140.

ticular failure associated with Addison's disease is quite uncommon and generally is associated with polyendocrine autoimmune failure associated with candidiasis and hypoparathyroidism.

(c) Hypoparathyroidism

Autoimmune hypoparathyroidism occurs mostly in children and adolescents, and is often associated with mucocutaneous candidiasis (Type I polyendocrine autoimmune disease). It is thus frequently associated with Addison's disease, and other organ-specific autoimmune diseases.[1]

The pathological picture is characterized by lymphocytic infiltration and atrophy. Anti-parathyroid antibodies and evidence for cell-mediated immunity have been demonstrated.[1]

(d) Hypophysitis

The subject of autoimmune hypophysitis has been summarized by Josse.[68] There are now over 16 cases of autoimmune hypophysitis reported, all in women between ages of 22 and 74 years. In many of these patients, the diagnosis was made at autopsy. A conspicuous feature of this condition has been its association with pregnancy and the post partum state. In 8 of the 16 reported cases the disease was detected following delivery, with the longest interval after gestation being 14 months. It is possible to speculate that cases that have been diagnosed as post partum Sheehan's syndrome may instead be examples of post partum autoimmune pituitary disease, developing insidiously during and after pregnancy.

The reason for this timing may relate to considerations discussed under the heading Postpartum Thyroiditis elsewhere in this volume. Another prominent feature of autoimmune lymphocytic hypophysitis has been its association with other organ-specific autoimmune disorders such as Hashimoto's thyroiditis, adrenalitis and pernicious anaemia.

(e) Polyendocrine Autoimmune Failure

Theoretically any patient with one expressed autoimmune endocrine disease showing serological reactivity with another organ should be considered as potentially belonging to the polyendocrinopathies.[69] While many of these target organs are indeed endocrine glands, other associated non-endocrine organ-specific autoimmune diseases which are associated in increased frequency include pernicious anemia, myasthenia gravis, Sjogren's disease, vitiligo, alopecia areata, chronic active hepatitis, idiopathic thrombocytopenic purpura and rheumatoid arthritis. Those patients with overt autoimmune disease of other organs would be considered definite examples. The classification of Neufeld and Blizzard[70] is of interest (Table 8).

It is of interest that of all of those categories listed in Table 8 only II and III are associated with definite HLA genes.[69] Category I which seems to be the most severe form of autoimmune polyglandular endocrine failure has not been shown to have any particular HLA type and generally occurs in children. Possibly in this condition the putative suppressor T lymphocyte defect is more severe and more non-specific than that seen in the other entities.

There are a variety of other more rare polyendocrine autoimmune syndromes, such as central diabetes insipidus, autoimmune enteropathy, autoimmunity to gut hormone-secreting cells, and autoimmunity directed against specific prolactin cells in the anterior pituitary. These latter entities have been discussed by Bottazzo and Doniach[69] in a recent interview.

Summary

The observation that all of the disorders listed on Table I have a close association with one another and are often associated with specific HLA genes, suggests a very similar pathogenesis for all of these entitities. It may well be that each disease has a separate gene, and each a separate organ-specific defect in immunoregulation. This author favors the hypothesis that that defect is an organ-specific abnormality in suppressor T lymphocyte function, specific for each disease. The fact that some persons develop two or more diseases may have to do with gene clustering, ie; the inheritance of more than one closely related gene. However, it is clear that much investigation needs to be done before our understanding of these diseases is clarified. There is obviously a great deal of excitement still to come.

REFERENCES

1. Volpe, R. Autoimmunity in the Endocrine System, Monographs in Endocrinology No. 20, Springer Verlag, Heidelberg, 1981.
2. Volpe, R. Autoimmunity in Endocrine Disease, Marcel Dekker, New York, 1985.
3. Davies, T.F. Autoimmune Endocrine Disease, Wiley, New York, 1983.
4. Pruzanski, W. General principles of immunity. In: Autoimmunity and Endocrine Disease, ed. by Volpe, R. Marcel Dekker, New York, pp. 1-31.
5. Volpe, R., Jansson, R, Karlsson, A. and Dahlberg, P.A. Thyrostatic drugs act through modulation of thyroid cell activity to induce remissions in Graves' disease. Clin. Endocrinol. (In press)
6. Burnet, F.M. Clonal selecation and after. In: Theoretical Immunology. Edited by Bell, G.I., Perelson, A.S. and Pimbley, G.H. Marcel Dekker, New York, 1979. pp. 63-85.
7. Roitt, I.M. Prevailing theories in autoimmune disorders. Triangle. 23:67-76. 1984.
8. Farid, N.R. and Bear, J.C. The major histocompatibility complex and endocrine disease. Endocrine Reviews 2:50-86.1981.

Table 8

Classification of Polyglandular Autoimmune Disease

I.	Candidiasis, hypoparathyroidism, Addison's disese (2 or 3 present)
II.	Addison's disease and thyroid autoimmune disease and/or insulin dependent diabetes mellitus
III.	a) Thyroid autoimmune disease and insulin dependent diabetes mellitus
	b) Thyroid autoimmune disease and pernicious anaemia
	c) Thyroid autoimmune disease and vitiligo and/or alpecia and/or other organ specific autoimmune diseases not falling into the above categories

Reproduced by permission from Neufeld and Blizzard, In: Autoimmune aspects of Endocrine Disorders, Ed. Pinchera, A. Academic Press, New York, 1980, pp.357-366.

9. Svejgaard, A., Platz, P. and Ryder, L.R. HLA and endocrine disease. In: Autoimmunity and Endocrine Disease, ed. Volpe, R. Marcel Dekker, New York, 1985. pp. 93-108.
10. McDevitt, H.E. and Benacevraf, B. Genetic control of specific immune responses. Adv. Immunol. 11:31-74. 1969.
11. Batchelor, J.R. Genetic role in autoimmunity. Triangle 23:77-83. 1984.
12. Bottazzo, G.F., Rujol-Borrell, R., Hanafusa, T. and Feldman, M. Role of aberrant HLA-DR expression and antigen presentation in induction of endocrine autoimmunity. Lancet 8359(2):1115-1119, 1983.
13. Iwatani, Y., Gerstein, H., Iitaka, M., Row, V.V. and Volpe, R. Thyrocyte HLA-DR expression induced by autologous Graves' lymphocytes and supernatants from mitogen-stimulated lymphocytes. Proc. 9th Internat. Thyroid Congr., Sao Paulo, Brazil, Sept 1-6, 1985. p. 192, Abstr. 303. Plenum Press: in press.
14. Farrar, J.J., Benjamin, W.R., Hilfiker, M.L., Howard, M., Farrar, W.L. and Fuller-Farrar, J. The biochemistry, biology and role of interleukin 2 in the induction of cytotoxic T cell and antibody-forming B cell responses. Immunol. Rev. 63:129-166, 1982.
15. Todd, I., Pujol-Borrell, R., Hammand, L.H., Bottazzo, G.F. and Feldmann, M. Interferon-8 induces HLA-DR expression by thyroid epithelium. Clin. Exp. Immunol. 61:265-270. 1985,
16. Iwatani, Y., Row, V.V. and Volpe, R. What prevents autoimmunity? Lancet 2:839-840, 1985.
17. Volpe, R. Autoimmune thyroid disease: a perspective. Molecular Biology and Medicine: in press.
18. Fentiman, I.S., Thomas, B.S., Balkwill, F.R., Rubens, R.D. and Hayward, J.L. Primary hypothyroidism associated with interferon therapy of breast cancer. Lancet 1:1166, 1985.
19. Burman, P., Karlsson, F.A., Oberg, K. and Alm, G. Autoimmune thyroid disease in interferon treated patients. Lancet 2:100-101, 1985.
20. Weetman, A.P. and McGregor, A.M. Autoimmune thyroid disease: developments in our understanding. Endocr. Rev. 5:309-355, 1984.
21. Burman, K.D. and Baker, J.R. Immune Mechanisms in Graves' disease. Endocrine Reviews 6:183-232, 1985.
22. Hashimoto, H. Zue Kenntnis der lymphomatosen Veranderung der Schilddruse (Struma lymphomatosa). Arch. Klin. Chir. 97:219-248, 1912.
23. Roitt, I.M., Doniach, D., Campbell, R.N. and Hudson, R.V. Autoantibodies in Hashimoto's disease (lymphadenoid goitre). Lancet 2:820-821, 1956.
24. Rose, N.R. and Witebsky, E. Studies on organ specificity. V. Changes in the thyroid glands of rabbits following active immunization with rabbit thyroid extracts. J. Immunol. 76:417-427, 1956.
25. Adams, D.D. and Purves, H.D. Abnormal responses in the assay of thyrotrophin. Univ. Otago Med. School Proc. 34:11-12, 1956.
26/McKenzie, J.M. Humoral factors in the pathogenesis of Graves' disease. Physiol. Rev. 48:252-310, 1968.
27. Volpe, R. and Row, V.V. Role of antigen-specific suppressor T lymphocytes in the pathogenesis of autoimmune thyroid disease. In: Autoimmunity and the Thyroid, ed. by Walfish, P.G., Wall, J.R. and Volpe, R. Academic Press, Orlando, Fla, 1985, pp. 79-84.
28. Grubeck-Loebenstein, B., Derfler, K., Kassal, H., Knapp, W., Krisch, K., Liszka, K., Smyth, P.H. and Waskhausl, W. Immunological features of nonimmunogenic hyperthyroidism. J. Clin. Endocrineol. Metab. 60:150-155, 1984.
29. Gerstein, H., Iwatani, Y., Iitaka, M., Row, V.V. and Volpe, R. Enumeration of T lymphocyte subsets in Graves' disease: decreased suppressor cells in severe hyperthyroidism. Proc. 9th Internat. Thyroid Congress, Sao Paulo, Brazil, Sept 1-6, 1985. Plenum Press: in press.
30. Editorial. Emotion and immunity. Lancet 2:133-134, 1985.
31. Okita, N., Row, V.V. and Volpe, R. Suppressor T lymphocyte deficiency in Graves' disease and Hashimoto's thyroiditis. J. Clin. Endocrinol. Metab. 52:528-533, 1981.
32. Okita, N., How, J., Topliss, D., Lewis, M., Row, V.V. and Volpe, R. Suppressor T lymphocyte dysfunction in Graves' disease: role of the H-2 histamine receptor bearing suppressor T lymphocytes. J. Clin. Endocrinol. Metab. 53:1002-1007, 1981.
33. Topliss, D.J., Okita, N., Lewis, M., Row, V.V. and Volpe, R. Allosuppressor T lymphocytes abolish migration inhibition factor production in autoimmune thyroid disease: evidence from radiosensitivity experiments. Clin. Endocrinol. 15:335-341, 1981.
34. Topliss, D.J., How, J., Lewis, M., Row, V.V. and Volpe, R. Evidence for cell-mediated immunity and specific suppressor T lymphocyte dysfunction in Graves' disease and diabetes mellitus. J. Clin. Endocrinol. Metab. 57:700-705, 1983.
35. Vento, S., Hegarty, J.E., Bottazzo, G.F., Macchia, E., Williams, R. and Eddlestone, A.L.W.F. Antigen-specific suppressor cell function in autoimmune chronic active hepatitis. Lancet 1:1200-1204, 1984.
36. Vento, S., O'Brien, C.J., Cundy, T., Williams, R. and Eddlestone, A L.W.F. T lymphocyte sensitization to discrete thyroid membrane antigens in patients with different autoimmune disorders. Proc. 7th European Immunologyh Meeting, Jerusalem, Israel, Sept 8-13, 1985, p. 205.
37. Noma, T., Yata, J., Shishiba, Y. and Inatsuki, B. In vitor detection of antithyroglobulin antibody forming cells from thelymphocytes of chronic thyroiditis patients and analysis of their regulation. Clin. Espl Immunol. 49:565-571, 1982.
38. Mori, H., Hamada, N. and De Groot, L.J. Studies in thyroglobulin-specific suppressor T cell function in autoimmune thyroid disease. J. Clin. Endocrinol. Metab. 61:306-312, 1985.
39. Tao, T.W., Gatenby, P.A., Leu, S.L., Pham, H. and Kriss, J.P. Helper and suppressor activities of lymphocyte subsets on antithyroglobulin production in vitro. J. Clin. Endocrinol. Metab. 61:520-524, 1985.
40. Benveniste, P., Row, V.V. and Volpe, R. Studies of the immunoregulation of thyroid autoantibody production in man. Cliln. Exp. Immunol. 61:274-282, 1985.
41. Ludgate, M.E., Ratanachaiyawong, S., Weetman, A P., Hall, R. and McGregor, A.M Failure to demonstrate cell-mediated immune responses to thyroid antigens in Graves' disease using in vitro assays of lymphokine mediating migration inhibition. J. Clin. Endocrinol. Metab. 60:98-102, 1985.
43. Weetman, A.P., Volkman, D.J., Burman, K.D., Gerrard, T.L. and Fauci, A.S. The in vitro regulation of human thyrocyte HLA-DR antigen expression. J. Clin Endocrinol. Metab. 61:817-824.
44. How, J., Topliss, D.J., Trakosch, C., Lewis, M., Row, V V. and Volpe, R. T lymphocyte sensitization and suppressor T lymphocyte defect in patients long after treatment for Graves' disease. Clin. Endocr. 18:61-72. 1983.
45. Weetman, A.P., McGregor, A M. and Hall, R. Evidence for an effect of antithyroid drugs on the natural history of Graves' disease. Clin. Endocrinol. 21:163-172, 1984.
46. Ratanachaiyawong, S. and McGregor, A.M. Immunosuppressive effects of antithyroid drugs. Clin. Endocr. Metab. 14:449-466, 1985.
47. Hamilton, R.D., Mayberry, W E., McConahey, W.M. and Hanson, K.C. Ophthalmopathy of Graves' disease: a comparison between patients treated surgically and patients treated with radiodine. Mayo Clin. Proc. 42:812-819. 1967.
47. Lewis, M., Topliss, D.J., Okita, N., How, J., Row, V.V. and Volpe, R. The etiology of endocrine exophthalmos. In: Clinical Immunology Update 1983. Ed. Franklin, E.C., Elsevier Biomedical, New York, pp. 261-280, 1983.
48. Gorman, C.A., Waller, R.R. and Dyer, J.A. The ye and orbit in thyroid disease. Raven Press, New York, 1984, pp. 1-341.
49. Volpe, R. Endocrine opthalmopathy. In: Cyclosporin in autoimmune disease, ed. Schindler, R., Springer Verlag, Berlin, 1985, pp. 223-228.
50. Eisenbarth, G.S. Autoimmune beta cell insuficiency - diabetes mellitus Type I. Triangle 23:111-124, 1984.
51. Rossini, A.A., Mordes, J.P. and Like, A.A. Immunology of insuliln-dependent diabetes mellitus. Ann. Rev. Immunol. 3:289-320, 1985.
52. Powers, A.C. and Eisenbarth, G.s. Autoimmunity to islet cells in diabetes mellitus. Ann. Rev. Med. 36:533-544, 1985.
53. Yoon, J.W., Austin, M., Anodera, T. and Notkins, A.L. Virus induced diabetes mellitus: isolation of a virus from the pancreas of a child with diabetic ketoacidosis. New Engl. J. Med. 300:1173-1179, 1979.
54. Gepts, W. The pathology of the pancreas in human diabetes. In: Immunology and diabetes, ed. Andreani, Al., DiMario, U., Federliln, K.F. and Heding L.G. Kimpton, London, 1984, pp.21-34.
53. Menser, M.A., Forrest, J.M and Bransby, J.M Rubella infection and diabetes mellitus. Lancet 1:57-61, 1987.
54. Spencer, K.M., Dean, B.M., Tern, A., Lister, J. and Bottazzo, G.F. Fluctuating islet cell antibodies in unaffected relatives of patients with insulin dependent diabetes. Lancet 1:764-,1984.
55. Lernmark, A and Baekkescov, S. Islet cell antibodies - theoretical and practicalk implications. Diabetologia 24:431-,1981.
56. Brogren, C.H. and Lernmark, A. Islet cell antibodies in diabetes. Clinics in Endocrinol. Metab. 11:409-430, 1982.
57. Mandrup-Poulsen, T. Studies of the molecular mechanisms of beta-cell destruction. Molecul. Biol. Med.: in press.
58. Baekkescov, S. Nielsen, J.H., Marner, B., Bilde, T., Ludvigsson, J. and Lernmark, A. Autoantibodies in newly diagnosed diabetic children. Immunoprecipitate-specific human islet cell proteins. Nature 198:167-169, 1982.
59. Bottazzo, G.F., Dean, B.M. McNally, J.M., McKay, E.H., Swift, P.G.F. and Gamble, D.R. In situ characterizationof autoimmune phenomena and expression of HLA molecules in the pancreas in diabetic insulitis. New Engl. J. Med. 313:353-360, 1985.
60. Nerup, J., Anderson, O.O., Bendinen, G., Egeberg, J. and Paulsen, J.E. Antipancreatic cellular hypersensitivity in diabetes mellitus. Diabetes 20:424-427, 1971.
61. Boitard, C., Debray-Sachs, M., Pouplard, A., Assan, R. and Hamburger, J. Lymphocytes from diabetes suppress insulin release in vitro. Diabetologia 21:41-, 1981.
62. Fairchild, R.S., Kyner, J.L. and Abdou, N.I. Suppressor cell dysfunction in insulin dependent diabetes. Diabetes (Supplem. 2) 29:52A (Abstr. 208), 1980.

(cont. on page 52)

Cyto·Pathology Associates

Consultation in Exfoliative Cytology

123 Edward St.
Toronto, Ont., M5G 1E7
Tel: 597-0539

Dr. A.E. Gray
Dr. R.C. Ross
Dr. D.W. Thompson
Dr. H.T. Van Patter

The Influence Of Soft Tissue Coverage On The Healing Of Tibial Fractures:

A Literature Review And Appraisal Of Current Surgical Techniques

Rex Verschuren, B.Sc. 8T7

Introduction

The most effective management of the soft tissue wounds associated with severe open tibial fractures is controversial. Often open tibial fractures can be associated with significant soft tissue loss and devascularization of the fracture fragments. The surgeon must first decide between leaving the bone exposed or covering it with soft tissue. Then, if electing for soft tissue coverage, the surgeon must choose between the various soft tissues available.

In this paper the influence of soft tissue coverage on the healing of tibial fractures will be discussed. Recent experimental evidence will be integrated with the past literature relevant to tibial fracture management. Case reports will be used to demonstrate the important problems facing clinicians in the management of soft tissue injuries associated with tibial fractures. The purpose of this paper will be to discuss the most effective management of the soft tissue wounds associated with open tibial fractures. The role of specific types of soft tissue coverage on tibial fracture healing will be investigated.

Problems with soft tissue coverage frequently affect the tibia because of its anatomy[14]. The tibia is a subcutaneous bone with little soft tissue coverage anteriorly. When fractured the tibia may be stripped of its overlying skin and periosteum. This compromises the blood supply to the outer cortex and decreases the rate of fracture union. Significant soft tissue injury with exposure of the underlying bone creates an ideal medium for bacterial colonization and the development of osteomyelitis which decreases the rate of fracture union.[5 6 11] For these reasons, the management of the soft tissue wounds associated with open tibial fractures has great clinical importance. A review of the methods of soft tissue coverage will be helpful in determining the optimum treatment method.

Fracture Management: Methods To Obtain Soft Tissue Coverage Of Exposed Tibial Bone

Open tibial fractures are often associated with soft tissue loss and devascularization of the fracture fragments. In the less severe tibial fractures where the periosteum is still relatively intact the surgeon may elect to leave the bone exposed and allow granulation tissue to form. A split thickness skin graft may then be successfully applied. Split thickness skin grafts do not increase the local blood flow to the underlying bone.[6] Many patients with skin grafts applied to exposed bone develop recurrent ulceration. Recurrent ulceration can require multiple readmissions and prolonged immobilization of the limb.

Relaxing incisions can be used to provide a full thickness skin flap. A longitudinal incision is made posteriorly in the skin of the calf and the skin flaps are pulled around over the anterior soft tissue defect to achieve closure. There is a risk of developing a long bipedicled skin slough with this method. The secondary defect caused by the relaxing incision usually requires skin grafting.[8 18] Therefore, the use of relaxing incisions is not recommended.

Local rotational flaps are usually inadequate due to the unyielding nature and poor vascularity of the pretibial skin. They also create a secondary defect. Cross leg pedicle skin flaps are not commonly used as they necessitate prolonged periods of immobilization, create a donor defect in the normal leg and, require good donor tissue which may not be available in the case of bilateral tibial fractures. The deficiencies of these methods of obtaining soft tissue coverage encouraged the development of the muscle flap.

Local rotational muscle flaps have been popularized by Ger.[4 5] When elevated with two knowledge of their vascular anatomy they provide an excellent blood supply to the underlying bone and seldom undergo necrosis. Their pliability allows them to conform to the underlying exposed bone surface. The risk of bacterial contamination beneath a muscle flap compared to a random skin flap has been shown to be decreased due to the improved local oxygenation.[15]

If there has been major soft tissue loss the use of a local muscle flap may not be possible. In these cases the development of microvascular surgery has played an important role. Free tissue elevated on its neurovascular pedicle may be obtained from a distant site and transferred to the area of soft tissue loss.[2] Free tissue transfers can consist of muscle[16 24] (eg. latissimus muscle flap), skin and subcutaneous tissue [2 3 17 23] (eg. groin flap), or muscle, subcutaneous tissue and skin[25] (eg. latissimus myocutaneous flap). The transfer of these tissues is performed at a single operation and if successful significantly shortens the period of hospitalization and immobilization.

The disadvantages of flap coverage include hematoma formation and infection, both of which may lead to the loss of the transferred tissue. In order to prevent infeaction the recipient site must be thoroughly debrided of all necrotic tissue and only viable muscle used to cover the bone.

The Influence Of Soft Tissue Coverage Of Fracture Healing: Experimental Investigation

The relationship between fracture healing and the quality of the surrounding soft tissue blood supply has been investigated.[7 10 13 14 17] It has been demonstrated that there is an

increase in the number and size of arterial vessels surrounding a fracture site.[10 22] It was noted that fracture healing was accompanied by the formation of numerous periosteal and "intraosseous" blood vessels. The increase in blood supply provided an environment rich in nutrients for osteoclastic and osteoblastic activity. Destruction of the periosteal blood supply has been shown to lead to nonunion of experimental fractures.[10] Subsequent investigations concluded that when the medullary circulation was disrupted by a displaced fracture, the periosteal circulation became the primary source of blood supply for fracture healing.[22]

The relationship of ischemic soft tissue to bone graft incorporation and osteotomy union has also been investigated.[22] It was found that ischemia of the muscle surrounding the osteotomy site leads to poor callus formation. This delayed bone graft incorporation and osteotomy union.[25]

One study[12] had shown that muscle flaps improve bone graft survival in irradiated tissue, however, little was known about the effect of muscle flap coverage on bone revascularization, new bone formation and fracture union in normal tissue. Subsequent investigations[13 21] using animal models, studied the influence of specific types of soft tissue coverage on fracture healing. These studies however, had not isolated the surounding soft tissue as the sole source blood supply to the underlying bone fragment. For this reason the following study[20] was undertaken.

The Influence Of Specific Types Of Soft Tissue On Fracture Healing

The purpose of this study was to create an animal model that would simulate a severe tibial fracture by disrupting both the medullary and periosteal blood supply to the tibia. With the nutrient artery and periosteal blood supply severely compromised, the only good source of blood would come from the surrounding soft tissues. A controlled comparison of the effects of muscle versus skin tissue coverage on fracture healing could then be evaluated.

This was accomplished by removing a two centimeter segment of mid diaphyseal bone of the canine tibia, resecting the periosteum, replacing the segment and securing it by internal fixation (Figure 1).

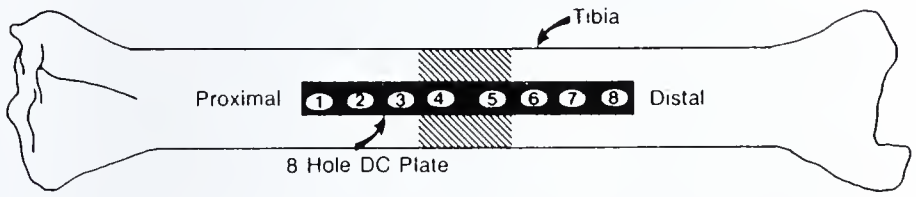


Figure 1 A two centimeter segment of canine tibial diaphysis was devascularized by removal from the animal. The segment was then anatomically reduced and fixed with a plate.

The fascia overlying the medial cortex was excised. The cranial tibialis muscle was also excised in the skin coverage group. The skin was closed over the tibia with multiple interrupted sutures. The tibia of animals in the skin coverage group was covered with periosteum and muscle posteriorly, the plate laterally and skin medially (Figure 2). In the muscle group the cranial tibialis muscle was mobilized to its origin with preservation of its vascular pedicle and rotated anteriorly to cover the devascularized tibial segment. The cranial tibialis muscle was then sutured to the posterior fascia. The skin was closed over the muscle flap. Therefore the tibia of animals in this group was covered with periosteum and muscle posteriorly, the plate laterally and the cranial tibialis muscle medially (Figure 2).

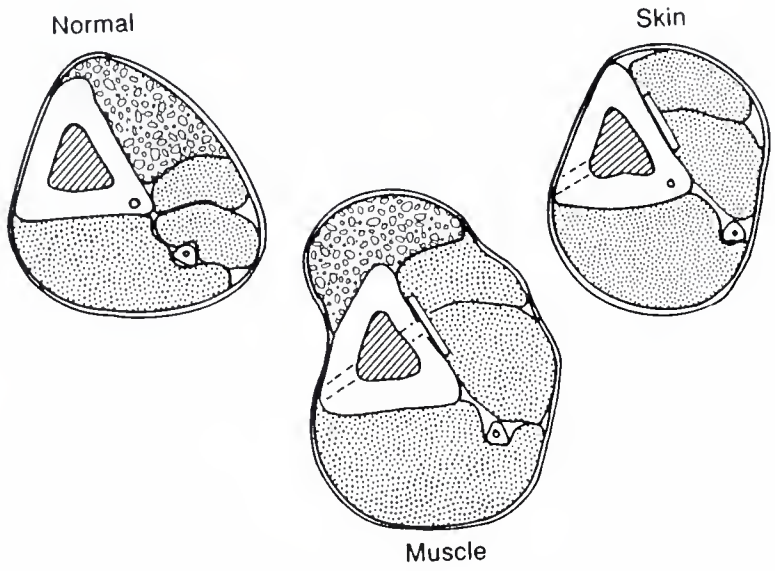


Figure 2 Cross sections of the leg through the segment of devascularized tibia. The muscle (irregular stippling represents the cranial tibialis muscle) is removed in the skin group and rotated over to the medial cortex in the muscle group.

After forty-two days the animals were sacrificed and both tibiae removed. Sections of bone from the devascvularized segment, forty microns in thickness were prepared.[19 20] The medial, lateral and posterior corticles were divided into six zones (Figure 3). Each zone was then subdivided into inner, middle and outer zone. Six microscopic fields were examined in each zone giving a total of fifty-four measurements per specimen. Mean values were obtained by averaging the values for the inner, middle and outer zones of each cortex separately.

Bone healing was assessed by three methods; cortical porosity, intracortical new bone formation (depth and amount) and callus morphometry.

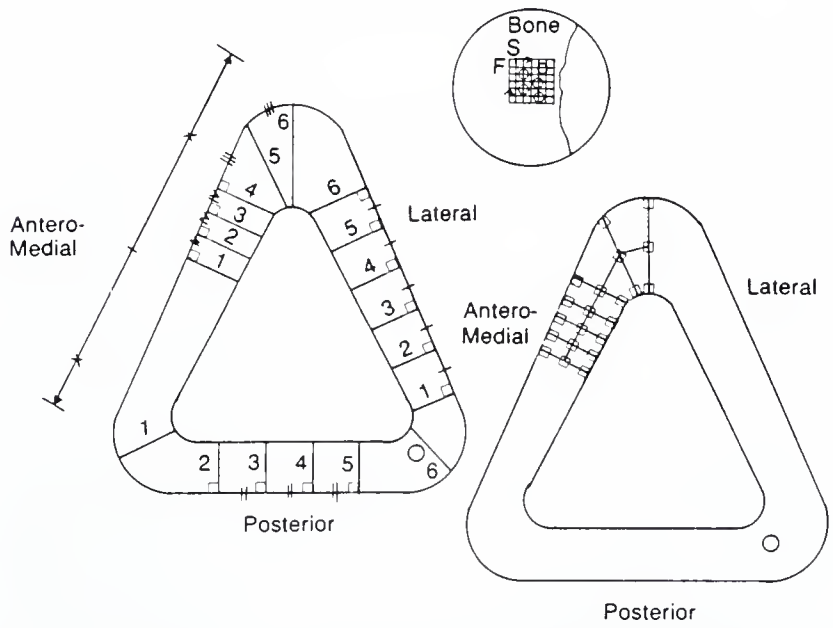


Figure 3 Cross sections of tibia showing the division of each cortex into six equal zones. Also shown is the division of each cortex into an inner, middle and outer zone creating a total of fifty-four fields of measurement.

Cortical Porosity

Measurements of both the operated and nonoperated tibia of each animal were made using a microscope fitted with a

camera lucida and a digitizing board. The data were analyzed with the aid of an IBM PC computer. The porosity data are expressed as a percentage of cortical bone area. Any increases in cortical porosity were interpreted as evidence of increased vascular penetration of the devascularized tibial cortex.

Intracortical New Bone Formation

Fluorochrome dyes were injected intravenously into the animals at twenty-one and forty-two days. These dyes were incorporated into the newly forming bone. The measurements were made using the same specimen, equipment (fitted with special lighting to cause the fluorochrome labels to fluoresce) and sampling techniques. The area of new bone formation was expressed as a ratio of the area of surface fluorescence to the total surface area of the haversian canals. For each specimen, the maximum depth of new bone formation was measured along the medial, lateral and posterior cortices.

Callus Morphometry

Sections one millimeter in thickness were cut from the centre of the removed bone segment. The specimens were photographed under polarized light to enhance the division between enveloping callus and cortical bone. The area of enveloping callus was measured for the posterior and medial cortex. There was no callus formation on the lateral cortex as it was covered by the plate. The area of the callus for each cortex was expressed relative to the area of original cortical bone. The measurements were made using the digital morphometry board and computer.

Experimental Results and Discussion

There was no significant difference found in the area of callus formation between the skin and muscle group around the posterior cortex. The amount of enveloping callus formation over the medial cortex was significantly increased in the muscle flap coverage group over the skin coverage group (Table 1). There was very little callus formation around the lateral cortex due to the plate.

The measurements of cortical porosity revealed that the greatest change in porosity occurred in the outer zones of the medial and posterior cortices (Figures 4a and 4b). There was no increase in the cortical porosity in the middle and inner zones of any of the cortices. The outer zone of the lateral cortex covered by the plate also showed no increase in porosity.

The porosity of the outer zones of the posterior cortex in both the skin and muscle group were significantly greater than the porosity of the control groups (Table 11). The porosity of the outer zone of the medial cortex in the muscle flap group was significantly greater than the corresponding zone of the medial cortex of the skin group (Figures 5a and 5b) (Table 11).

The greatest amount of intracortical new bone formation at twenty-one and forty-two days postoperation occurred along the posterior cortices of both groups. Very small amounts of new bone formation occurred in the middle zone and endosteal surface of the cortex. The only significant difference in intracortical new bone formation between

TABLE I

LOCATION AND AREA* OF ENVELOPING CALLUS SURROUNDING TIBIAL CORTEX

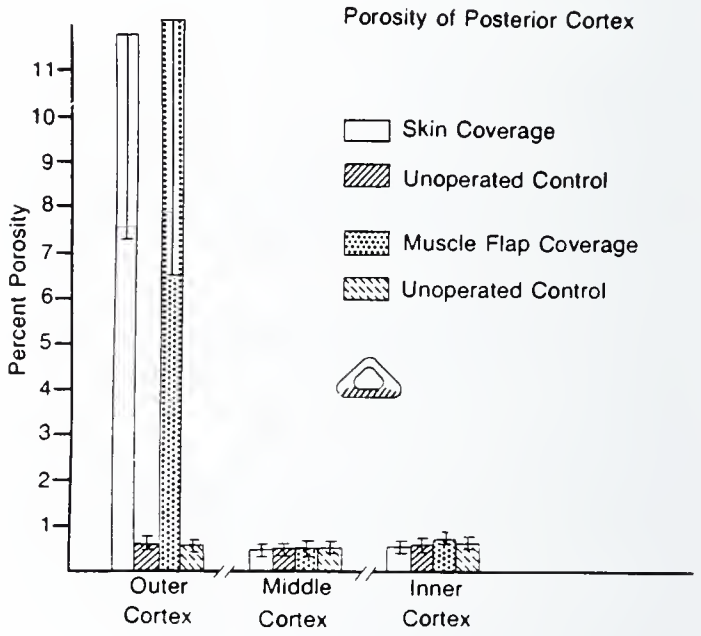
Location	Skin Coverage N = 7	Muscle Flap Coverage N = 6	Probability +
Posterior Cortex	23.81 ± 10.35	13.50 ± 9.20	NS
Lateral Cortex #	0.03 ± 0.08	0	-
Medial Cortex &	1.13 ± 0.92	4.75 ± 2.16	$p < 0.05$

* Area = $\frac{\text{Area of enveloping callus adjacent to cortex}}{\text{Area of original cortical bone}}$

\+ unpaired test, NS = not significant

\# beneath plate

& area of muscle coverage in flap group



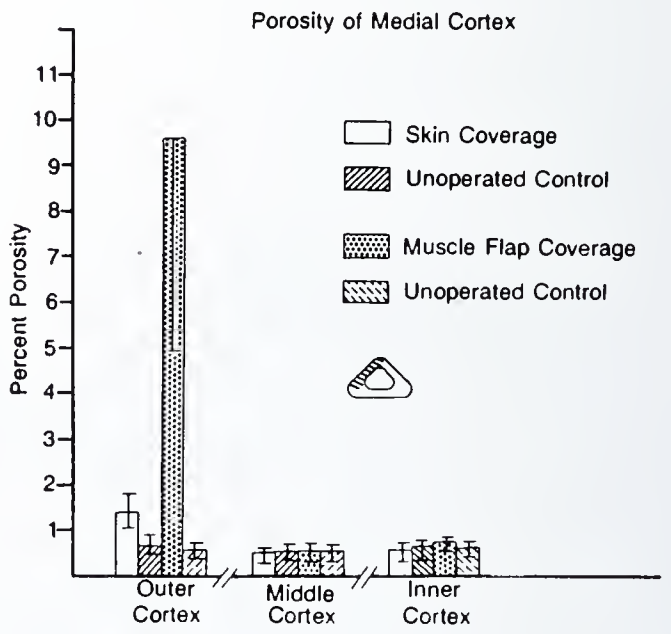


Figure 4a and 4b Percent porosity of the outer, middle and inner cortical zones.
Figure 4a Posterior cortex.
Figure 4b Medial cortex.

TABLE II

CORTICAL POROSITY*

All Measurements From Outer Cortex	Skin Coverage N = 7	Muscle Flap Coverage N = 6	Probability +
Posterior Cortex	11.96 ± 4.62	11.20 ± 4.68	NS
Control	.613 ± .106	.594 ± .120	NS
Lateral Cortex #	.168 ± .007	.202 ± .035	$p < 0.05$
Control	.546 ± .047	.541 ± .058	NS
Medial Cortex &	1.43 ± .581	9.61 ± 4.66	$p < 0.005$
Control	.673 ± 1.57	.575 ± .072	NS

* percent porosity

Figure 5a Cross section of tibia from an animal in the skin coverage group. There is callus formation over the posterior cortex. There is an increase in porosity of the outer zone of the posterior cortex. There is some formation of callus over the anterior crest of the tibia. The medial and lateral cortices show no increase in porosity (x4).

Figure 5b Cross section of tibia from an animal in the musacle coverage group. Callus formation is seen over the posterior and medial cortices. The porosity of both the posterior and medial outer cortices has increased (x4).

the muscle and skin coverage groups occurred in the outer zone of the medial cortex (Table 111).

The maximum depth of new bone formation was greatest in the posterior cortices of both groups. Again the only significant difference in the maximum depth of new bone formation between the muscle and skin group, was found in the medial cortex (Table 1V).

These results consistently demonstrated that muscle coverage of exposed tibial bone is superior to skin coverage in terms of encouraging the revascularization and repair of devascularized segments of canine tibial cortex. The preceeding study emphasized the influence of muscle flap coverage on fracture healing. The following clinical cases further emphasize the importance of soft tissue coverage on the healing of open tibial fractures.

TABLE III

NEW BONE FORMATION* IN OUTER ZONE OF TIBIAL CORTEX

Location		Skin Coverage N = 7	Muscle Flap Coverage N = 6	Probability +
Posterior Cortex	21 Days	25.04 ±10.64	22.49 ±13.54	NS
	Control	9.27 ±10.54	4.72 ± 5.70	NS
	42 Days	43.89 ±15.37	42.16 ±15.23	NS
	Control	17.09 ±19.24	5.09 ± 4.90	NS
Lateral Cortex #	21 Days	.901 ± 1.54	0	-
	Control	.900 ± 3.80	8.00 ± 9.93	NS
	42 Days	.985 ± 1.68	0	-
	Control	12.04 ± 6.63	8.08 ± 8.83	NS
Medial Cortex &	21 Days	7.29 ± 7.18	21.41 ± 6.13	$p < 0.05$
	Control	15.48 ±11.11	13.28 ± 17.53	NS
	42 Days	15.64 ±16.06	39.46 ± 11.76	$p < 0.05$
	Control	19.99 ±12.24	16.33 ± 22.84	NS

* $\frac{\text{Area of Surface Fluorescence}}{\text{Surface Area}}$

TABLE IV

MAXIMUM DEPTH OF NEW BONE FORMATION*

Location	Skin Coverage N = 7	Muscle Flap Coverage N = 6	Probability +
Posterior Cortex	0.987 ±0.125	1.031 ±0.119	NS
Lateral Cortex#	0.196 ±0.051	0.114 ±0.115	NS
Medial Cortex&	0.469 ±0.147	0.957 ±0.148	$p < 0.001$

* Depth in mm at 42 days

Clincal Cases

CASE 1: A 30 year old male was involved in a motorcycle accident. Examination revealed an open type III[1 9] fracture of the left tibia and fibula, a fracture of the lateral epicondyle of the left humerus, a fracature of the pelvis through the left SI joint, disruption of the symphysis pubis, fractures of the right superior and inferior pubic rami and multiple abrasions. On admission he underwent debridement of the open fractures. Exploration revealed a four part comminuted fracture of the mid shaft of the tibia. The fragments were interlocked and anatomically reduced with interfragmentary compression screws. An external fixator was also applied with two pins above and two pins below the proximal and distal fragment sites with a quadrilateral frame (Figures 6a, 6b and 6c). The wound was packed open. The dressing was changed under general anesthesia 72 hours after injury. The tissues appeared healthy. Seven days later another operative procedure was performed in which the medial portion of the left soleus muscle and the medial head of the gastronemius muscle were transferred over the exposed tibia (Figure 7). At one month the external fixator was removed (Figure 8). There was no evidence of infection and

reepithelialization had occurred. The leg was put in cast and the patient was told to remain nonweight bearing for three weeks. Subsequently the patient began weight bearing (Figure 9). His soft tissue defect has healed (Figure 10) and there is a good range of motion in both the ankle and knee joints.

Figure 6a Case 1; Reduction of compound open fracture by internal and external fixation.

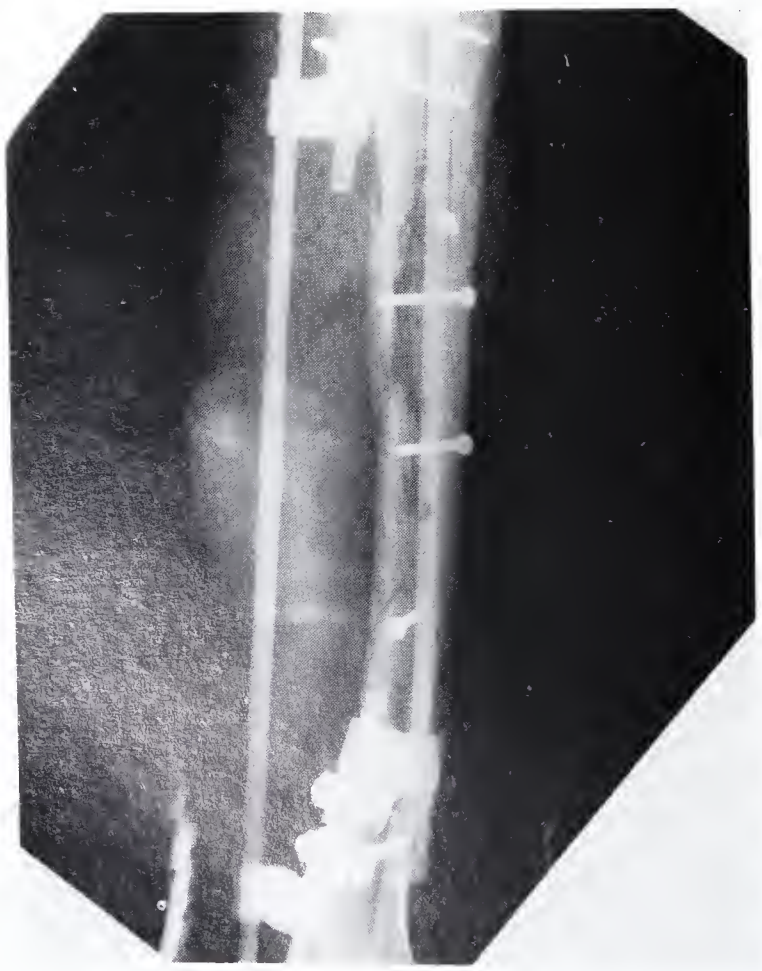


Figure 6b and 6c Roentgenograms of left tibia postoperatively showing internal fixation by interfragmentary compression screws and external fixation with a quadrilateral frame.

Figure 7 Transfer of the medial portion of the left soleus muscle and the medial head of the gastronemius muscle to the fracture site 8 days after admission.

Figure 8 Left tibia at 1 month after admission.

Figure 9 Left tibia at 4 ½ months after admission.

Figure 10 Left tibia at 4 ½ months showing good coverage of the previously exposed bone with viable tissue.

Figure 11 Case 2: Photograph upon admission of the right lower limb of a 27 year old man involved in a motorcycle accident. A large open defect over the tibia and fibula with extensive soft tissue destruction is seen.

CASE 2: This 27 year old male was also involved in a motorcycle accident. Examination revealed a large open wound of the right lower leg over the tibia (Figure 11). The fracture consisted of two main fragments proximal and distal to a large butterfly fragment on the lateral side. This fragment had protruded through the wound. The wound was debrided. The fractures were then reduced. The two main fragments were held with an external fixator. The butterfly fragment was then reduced and fixed to the two main fragments with two interfragmentary cortical screws with washers. Post reduction examination showed anatomic reduction of the fractures with palpable posterior tibial and dorsalis pedis pulses. The wound was irrigated, left open, and dressed with Softa-Tulle and moist saline compresses. The leg was stabilized in a posterior slab with a bulky pressure dressing down to the toes. Six days later a cancellous graft was taken from the right greater trochanter and packed posteromedially and posterolaterally around the fracture site. Two weeks later examination revealed a well stabilized fracture with an open soft tissue defect and exposed bone at the mid-portion of the tibia. The patient refused skin grafting and the defect was left to heal secondarily. Three weeks later, examination revealed drainage at the fracture site. The patient was then taken to the operating room where the external fixator was removed and the surrounding soft tissue debrided. The fracture was longitudinally stable with slight instability to valgus stress. A skin graft was transferred from the anterolateral aspect of the right hip and placed over the open wound. Eighteen days following this skin graft procedure the wound was found to be draining a foul-smelling discharge. Cultures grew Pseudomonos aeruginosa. The skin graft had become infected and ischemia of the butterfly fragment was noted. The necrotic bone was debrided and dressed, and the patient was transferred to St. Michael's Hospital in Toronto. The admitting diagnosis was osteomyelitis of the right tibia. Examination there revealed some evidence of bony union of the posterior tibia. The patient was taken to the operating room for bone grafting. The tibia was approached posteriorly through intact soft tissue. A bone graft was taken from the right posterior iliac crest and packed along the posterior aspect of the tibia as well as between the tibia and fibula along the interosseus membrane. Three days later a split thickness skin graft was taken from the right anterior thigh and grafted over the open defect. Roentgenograms showed good alignment of the tibia. The knee and ankle joints were parallel with 10 degrees of anterior bowing (Figure 12). The patient was discharged after one week (78 days following initial injury) and told to remain nonweight bearing for one month. He is now bearing full weight on the limb. There is a small open area over the anterior aspect of the tibia which is still draining. This may require skin grafting. His gait has improved and he has good range of motion in the knee but lacks some dorsiflexion of the ankle.

Figure 12: Roentgenogram 78 days after admission. There is good alignment of the tibia. The knee and ankle joints are parallel with 10 of anterior bowing.

Discussion

The goals of the reconstructive surgeon in the evaluation and treatment of open tibial fractures are as follows:
1) to prevent infection, and
2) to stabilize the fracture fragments and surrounding soft tissues
3) to achieve fracture union

Case 1 is an excellent example of the proper management of a severe open tibial fracture. The adequate debridement of all nonviable tissue and the early coverage of the open wound with viable soft tissue decreased the possibility of infection. In Case 2 however, the patient refused soft tissue coverage. The wound was left to heal secondarily by granulation tissue and subsequently became infected. When osteomyelitis developed, numerous debridements and a bone graft had to be performed until a viable recipient site for the transferred tissue could be obtained. This led to prolonged immobilization of the limb in hospital.

Each patient must be assessed individually as to which method of soft tissue coverage is most appropriate. Soft tissue coverage and bony reconstruction can be considered in only a viable, noninfected, stabilized limb. Management will depend upon the type of bone injury[1 9] the amount of soft tissue destruction, the presence of complicating factors such as infection or vascular disruption and, the availability of local and distant soft tissue for coverage.

Summary

Newly acquired knowledge regarding the effects of muscle coverage on bone healing has important clinical implications. Muscle coverage has been shown experimentally and clinically to stimulate the revascularization and repair of devascularized tibial bone. Optimal soft tissue coverage of open fractures should lead to shortened hospitalization of the patient due to earlier fracture union, decreased infection rate and earlier functional restoration of the damaged limb. This is beneficial in terms of the mental state of the patient, time away from work and reduced hospital costs.

Acknowledgements

The author would like to thank Dr. Robin Richards, Orthopaedic Division, Department of Surgery and Dr. Emil Orsini, Orthopaedic Resident, Department of Surgery, St. Michael's Hospital, Toronto for their assistance and kind support.

REFERENCES

1. Bosse, M.J., Burgess A.R., Brumback, R.J.; Evaluation and Treatment of High Energy Open Tibial Fractures. Advances in Orthopaedic Surgery. July-Aug 84, Volume 861. 3.
4. Ger, R.: The Management of Pretibial Skin Loss. Surgery. 63:757, 1968
5. Ger, R.: The Management of Open Fracture of the Tibia With Skin Loss. J. Trauma. 10:112, 1970.
6. Ger, R.: Muscle transposition for treatment and prevention of chronic post-traumatic osteomyelitis of the tibia. J. Bone Joint Surgery. 59A:784, 1977.
7. Gothman, L: Arterial changes in experimental fractures of the rabbit's tibia treated with intramedullary nailing: A microangiographic study. Acta Chir Scand 120:289, 1960.
8. Gregory,C.F.: Open Fracture. In Rockwood, C.A., Green, D.P. (Eds): Fractures, J.B. Lippincott, Philadelphia, 1975, pp. 119-155.
9. Gustilo, R.B., Anderson, J.T.: Prevention of Infection in the Treatment of One thousand and Twenty-five Open Fractures of Long Bones. J. Bone Joint Surg. 58A:453, 1976.
10. Kolodny, A: The periosteal blood supply and healing of fractures: Experimental study. J Bone Joint Surg 5:698, 1923.
11. Leach, R.E.: Fractures of the Tibia. In Rockwood, C.A., Green D.P. (Eds): Fractures. J.B. Lippincott, Philadelphia, 1975 pp. 1285-1359.
12. Lukash, F.N., Zingaro, E.A., Salig, J.: The Survival of Free Nonvascularized Bone Grafts in Irradiated Areas by Wrapping in Muscle Flaps. Plast. Recon. Surg. 6:783, 1984.
13. Mahoney, J.L., Richards, R.R., The Influence of Soft Tissue Coverage the Healing of Bone. Surgical Forum 34:610, 1983.
14. MacNab,I, DeHaas, W.G.: The Role of Periosteal Blood Supply in the Healing of Fractures of the Tibia. Clin. Orthop. 105:27, 1974.
15. Mathes, S.J., Alpert,B.S., al Chang, N.: Use of the Muscle Flap in Chronic Osteomyelitis: Experimental and Clinical Correlation. Plast Reconstr. Surg. 69:815, 1982.
16. May, J.W., Lukash, F.N., Gauilo, G.G. III.: Latissimus Dorsi Free Muscle Flap in Lower Extremity Reconstruction. Plast. Reconstr. Surg. 68:603, 1981.
17. May, J.W., Gallico, G.G., Lukash, F.M.: Microvascular Transfer of Free Tissue for Closure of Bone Wounds of the Distal Lower Extremity. N. Engl. J. Med 306:253, 1982.
18. Morley, G.H.: Application of Plastic Surgery to Care of the Injured. Br. Med. J. 1:823, 1966.
19. Recker, R.R.: Bone Histomorphometry: Techniques and Interpretation, pp. Boca Raton, Florida, C.R.C. Press,
20. Richards, R.R., Orsini, E.C., Mahoney, J.L., Verschuren,R.: The Influence of Muscle Flap Coverage on the Incorporation of Canine Diaphyseal Bone Grafts. (In preparation).
21. Richards, R.R., Mahoney, J.L., Minas, T.: The Influence of Soft Tissue Coverage on the Healing of Defects in Canine Diaphyseal Bone. Accepted for publication in Ann. Plast. Surg.
22. Rhinelander, R.W.: Microangiography in Bone Healing, II. Displaced Closed Fracture. J.Bone Joint Surg. 50A:643, 1968.
23. Serafin, D., Georgiade, N.G.,Smith D.H.: Comparison of Free Flaps with Pedicled Flaps for Coverage of Defects of the Leg or Foot. Plast. Reconstr. Surg. 59:492, 1977.
24. Vasconez, L.O., Bostwick, J., McGraw, J.: Coverage of Exposed Bone by Muscle Transposition and Skin Grafting. Plast. Recons. Surg. 53:526, 1974.
25. Stern, P.J., Neale, H.W., Gregory, R.O., McDonough, J.J.: Functional Reconstruction of an Extremity by Free Tissue Transfer of the Latissimus Dorsi. J. Bone Joint Surg. 65A:729, 1983.

For All Medical Students
Address UofT
Date October 84

℞ The finest in diagnostic and medical products, all on display in our showroom. — Just waiting for you.

Some Of Our Quality Brands:
Welch Allyn
Taylor (Tycos)
3M (Littmann)
Baum
Ritter
Miltex Instruments
Burdick

Take the subway — Osgoode Stop
10% discount with student card

Hours: 9:00 — 5:00
WHITE CROSS SURGICAL INSTRUMENTS LTD.
241 Richmond St. W., Toronto. M5V 2W3 (Tel. 598-4571)
5155 Timberlea Blvd., Mississauga (Tel. 625-2112)

BEST WISHES TO THE GRADUATES OF 86.

Alpha Laboratories Inc.

ANALYSIS AND RESEARCH IN
MEDICAL, PHARMACEUTICAL FOOD AND COSMETICS

DR. C. JOSEPH KURIAN
449-2166

285 LESMILL ROAD
DON MILLS, ONTARIO

Management of Meniscal Cysts By Arthroscopic Surgery

Jay S. Wunder 8T6

Abstract

Five patients with cysts of the menisci of the knee joint underwent arthroscopy. In each case, the cyst was found to be associated with a torn meniscus. Treatment involved partial meniscectomy and cyst decompression using arthroscopy. The clinical relevance of this technique is that a peripheral rim of meniscus is left intact, thus reducing the likelihood of the degenerative change commonly seen with total meniscectomy.

INTRODUCTION

The first description of cysts of the semilunar cartilages of the knee dates back to 1883. Since then, there have been numerous studies on the topic, but there still remains controversy over pathogenesis and treatment.

In some unusual circumstances, meniscal cysts have disappeared spontaneously, but most persist and gradually increase in size. These cysts are treated:

1. if they are symptomatic
2. if there are symptoms of an associated meniscal tear, and
3. to prevent the long-term complication of monocompartmental osteoarthritis

Suggested treatments have included cyst aspiration, arthrotomy with total meniscectomy and cyst excision, cyst excision alone, and partial meniscectomy by arthroscopy. Unfortunately, no specific treatment has been shown to be more efficacious than any other.

The first proposed treatment for meniscal cysts involved cyst aspiration alone. This fell into disuse due to the high rate of recurrence.

The commonly accepted management for this condition is complete excision of the cyst and meniscus. [2 3 5 6 9] Although this is a definitive treatment, it must be remembered that the menisci play an important role in lubrication and nourishment of articular cartilage, weight bearing, shock absorbing, stability and rotation of the knee.[15] Complete removal can be followed by instability and degenerative arthritis, the amount of articular cartilage damage being proportional to the amount of meniscus removed.[6]

In one study, Flynn and Kelly divided their patients into two groups.[8] Those in the first group were found to have a meniscal cyst with an otherwise intact meniscus. They were treated by local excision of the cyst only. The remainder had a torn meniscus in association with the cyst, and were treated by total meniscectomy. Those managed by cyst excision alone had no recurrences, and a considerably shorter period of rehabilitation. The advantage of this approach is that the meniscus is preserved. The main disadvantage is that other authors have reported a high recurrence rate.[3 13]

The latest treatment for meniscal cysts, suggested by this author, is partial meniscectomy and cyst decompression under arthroscopic control. This procedure leaves an intact peripheral rim of meniscus to provide some stability. In a study done by Ferriter and Nisonson, using a similar technique, it was reported that all cysts and related symptoms disappeared without recurrence.[7]

Meniscal cysts are not an uncommon disorder but are easily overlooked in diagnosing knee pathology. According to Smillie's series of 10,000 meniscectomies, 71.2 percent were medial and 28.8 percent were lateral.[15] Of those 10,000, 738 (7.38%) showed cystic formation. Although this study reported cystic formation in a ratio of 3 lateral:1 medial, it has been shown elsewhere to be as high as 5:1.[16] Males with this condition outnumber females 2:1-3:1, with the typical patient being a young adult male of average age 30 years.[5 16]

Meniscal cysts usually present with the clinical triad described by Bonnin as:

MEDICAL MART
SUPPLIES LIMITED

1224 DUNDAS STREET E., UNIT 28
MISSISSAUGA, ONTARIO, CANADA
L4Y 4A2 PH. (416) 276-4800
MEDIWATTS 1-800-268-2848 (ONT. ONLY),
TELEX 06-960218

PHYSICIAN STUDENTS SUPPLIES
A ONE STOP SUPERMARKET
FOR ALL YOUR OFFICE NEEDS

- Welch Allyn Diagnostic
- Treatment Cabinets
- Taylor & Baum B P Units
- Littmann Stethoscope
- B-D Syringes & Needles
- Step Stools
- Surgeon's Stools
- Exam Tables
- Scales
- Dressings

Let our experienced trade professional assist in your requirements

VISIT OUR LARGE MODERN SHOWROOM

HOURS: 9:00 - 5:00 Mon., Tues., Wed.
9:00 - 7:00 Thurs. 9:00 - 6:00 Fri.

1. an aching knee joint, worse with activity and at night, better with rest
2. pain localized by the patient to a small area over the joint line, and
3. a visible and palpable swelling in the same area which is tender.[3]

Less frequent complaints are recurrent effusion, locking, clicking, instability and decreased range of motion. A history of injury can be elicited from 30%-70% of patient presenting with a meniscal cyst.35 The trauma is more often endogenous (e.g. twisting, squatting), than exogenous (e.g. direct blow to the knee).

The cystic swelling is usually noted anterior to the fibular collateral ligament with the knee in 45 degrees of flexion. It commonly changes in size with different positions of the knee, and may disappear in full flexion or extension. An important diagnostic sign is that the swelling remains at the level of the joint line with knee movement.[2] The cyst is fluctuant and tender. Other evidence of a meniscal tear may be present. Medial cysts are usually larger than lateral ones because medial ones can expand through the capsule, whereas on the lateral side an intracapsular space exists which tends to contain the cyst.

Although the diagnosis of a joint line swelling of the knee as a meniscal cyst is usually obvious, other conditions must be considered in the differential diagnosis. An exostosis with an overlying bursa is usually found in older individuals with generalized joint involvement, is often bilateral, and is apparent on x-ray. A pedunculated tag of a torn meniscus can often be made to disappear with certain joint movements, and other signs of a torn meniscus may be evident. A loose body presenting as a joint line swelling may be difficult to diagnose, especially if radiolucent, as it will not show up on x-ray. An enlarged anserine bursa must be considered if there is medial joint line swelling. Often the semimembranosus tendon can be felt crossing.[6] Rarely, the bursa between the fibular collateral ligament and the lateral meniscus is enlarged. Other space occupying lesions such as ganglions, lipomas, villonodular synovitis and fibromas must also be considered.

Numerous theories have been proposed, but the etiology of meniscal cysts is still unclear. The main theories concern a) trauma, and b) congenital development.

The traumatic theory, first proposed by Ebner and later modified by Taylor states that a direct injury produces a contusion of the meniscus which is followed by mucinoid degeneration.[2] The high incidence of trauma preceding the onset of meniscal cysts (30%-70%), and the finding that 50%-100% of cysts are associated with meniscal damage, lend support to this theory.[1 3 5 10 16] Smillie has discounted that the original violence creates both the tear and the cyst.[15] Instead, he proposes that the trauma, usually endogenous, initiates a degenerative process which leads to cyst formation. This produces a point of abnormal fixation of them meniscus which makes it more susceptible to a tear. Although tears are more common on the medial side, cystic degenerationis more common laterally. This can be explained since: 1) the lateral meniscus carries 70 percent of the load across its joint versus 50 percent for the medial meniscus; and 2) the lateral meniscus, due to its external position and greater mobility is more exposed to direct and rotational trauma, both of them tend to produce degenerative lesions in its periphery.[14 15] The medial meniscus, due to its firmer attachements, tends to sustain tears in response to similar trauma.[5]

Ollerenshaw first suggested that inclusions of synovial tissue are incorporated within the fibrocartilage of the menisci during development, and an initiating factor, such as trauma, leads to cyst formation.[13] It has been shown by McDermott that the entire mensicus is covered with synovial cells during development, but after birth these cells are lost from the avascular portion of the cartillage.[12] During the transition period, some cells may be trapped within the fibrocartillage. King's study demonstrated that the lining cells of the cyst were actively secreting.[11] This supports the cyst as being developmental and not degenerative in nature.

MATERIALS AND METHODS

This is a retrospective case review of five patients presenting between 1980 and 1985, with the signs and symptoms of a meniscal cyst. Probably by chance, all involved the right knee (Table 1). Three patients were male and two were female. Their ages ranged from 18-51. Four of the patients had lateral cysts, and one had a medial cyst. Three gave a history of previous trauma: one with a repaired torn discoid lateral meniscus; another with a previously repaired radial tear of the lateral meniscus sustained after a direct sports injury. All had at least two symptoms from the triad described by Bonnin.[3] As well, one complained of instabililty, while two others suffered from recurrent effusions. The duration of symptoms ranged from three months to three years. Radiographic findings were normal except for the two patients with effusions: one had evidence of soft-tissue swelling, while the other had an area of fibrous dysplasia in the distal femur, but with a normal joint.

All patients underwent examination under anaesthesia, and subsequently were treated by arthroscopy. The lateral cysts were found to be associated with a tear in the middle-third of the meniscus, while the medial cyst had a posterior horn tear. In each case, the tear was debrided, thus exposing the track leading to the cyst in the periphery of the meniscus. With direct pressure applied over the cyst, numerous globules of fluid were expressed into the joint, thus indicating that adequate decompression of the cyst had been achieved. The joint was lavaged with saline before closure.

CASE HISTORY

Patient 2 is a 26 year old professional football player who injured his right knee in midseason. Within one month, he developed a slowly enlarging tender swelling over the lateral aspect of his right knee. He complained of an aching knee with activity. There was no clicking, locking, instability or effusion, and x-rays were normal. He received no treatment and functioned well despite the enlarging meniscal cyst, playing out the rest of the football season. In the off-season, he underwent arthroscopy which revealed a radial tear of the right lateral meniscus extending to within 2 mm. of the periphery in its middle one-third, plus a small flap tear of the anterior horn. Both tears were debrided,

TABLE I - CASE HISTORIES OF PATIENTS WITH MENISCAL CYSTS

D = instability E = recurrent effusions

Case	Age	Sex	Location	Previous Trauma	Symptoms	Duration of Symptoms	Xray	Additional Pathology	Follow-Up
1	18	M	right knee, lateral	- repaired right torn discoid lateral meniscus 2 yrs. before cyst	A, C, D	2 months	normal	- horizontal cleavage tear middle one-third	cyst and symptoms still present 5 1/2 yrs post-op
2	26	M	right knee, lateral	- none	A, B, C	2 months	normal	- radial tear middle one-third and flap tear anterior horn	asymptomatic 4 yrs. post-op
3	33	F	right knee, lateral	- none	A, C	2 years	normal	- radial tear middle one-third and slight fragmentation anterior horn	asymptomatic 2 yrs. post-op
4	19	M	right knee, lateral	- direct sports injury 4 months before cyst; radial tear lateral meniscus treated by saucerization 2 months before cyst	A, B, C, E	7 months	fibrous Dysplastic defect of distal femur posteriorly; normal joint	- repeat radial tear middle one-third and new posterior horn tear	asymptomatic 1 yr. post-op
5	51	F	right knee, medial	- none	A, B, C, E	3 years	soft tissue swelling	-posterior horn tear with flap and horizontal cleavage components	symptom free 6 months post-op

and a track from the site of the radial tear to the cyst was exposed. During decompression, gelatinous bubbles of fluid came into the joint, indicating adequate cyst decompression. One month after surgery, he still had a mild effusion and complained of slight tenderness on full extension. Two months later, he returned to football. Three and a half years post-surgery he is asymptomatic and still playing professionally.

RESULTS

One recurrence of the cyst has been noted. The shortest follow-up has been six months, and the longest 5½ years. Patients all left the hospitial on the same day as the arthroscopy and were back at work within a few days.

The four most recently treated patients all had successful decompressions without recurrence. All received the same treatment, are asymptomatic now, and are expected to remain the same in the future.

The only recurrence occurred in the first patient treated by this approach. Two facts may be implicated in this failure. Firstly, arthoscopy is an evolving technique, and since this patient was treated more than three years before the others, the technical skill may not have been as advanced at that time. Also, the fact that this patient had a tear of the same discoid lateral meniscus repaired two years previously may be significant.

DISCUSSION

The semilunar cartilages are indispensible structures of the knee joint, playing an integral role in normal joint function. Their total removal following rupture can be complicated by chronic instability and degenerative arthritis and thus should be avoided. This study proposes that partial meniscectomy and cyst decompression under arthroscopic control is a preferable treatment for meniscal cysts.

The four main advantages of this treatment are:

1) the cyst is decompressed
2) long-term complications of the meniscectomy are reduced
3) the procedure is relatively simple and can be carried out on an out-patient basis and
4) the clinical results to date are good

In this study, and that by Ferriter and Nisonson, all cysts were associated with a meniscal tear.[7] The proposed mechanism of cyst enlargement is believed to be the forcing of joint fluid into the meniscal tissue on weight-bearing, which is prevented from escaping since the tear acts as a one-way valve. With repeated activity, the cyst increases in size. Debriding the tear removes the one-way valve effect and allows the fluid to drain from the cyst. This results in a reduction in the size of the cyst and prevents recurrence if the communicating channel is adequately opened.

An important aspect of this treatment is that a peripheral rim of meniscus is left intact. Burke et al have shown that following partial meniscectomy, a peripheral rim of meniscus provides a significant load-bearing function which results in a more normal pressure distribution pattern than occurs with a total meniscectomy.[4] This reduces the likelihood of the development of monocompartmental osteoarthritis, a common complication of total

meniscectomy. More importantly, good clinical results have been reported with this procedure. In the follow-up of this study, and that by Ferriter and Nisonson, twenty-two patients reported complete disappearance of the signs and symptoms of the cyst, with only one recurrence.[7] Also, all patient left the hospital the same day the arthroscopy was performed, and had a significantly reduced period of rehabilitation and time off work.

Acknowledgements

Special thanks to Dr. R.W. Jackson and Miss Kathy McLaughlin of the Orthopaedic and Arthritic Hospital for their help in the preparation of this article.

REFERENCES

1. Barrie, H.J.: The pathogenesis and significance of meniscal cysts. The Journal of Bone and Joint Surgery. 61B(2):184, 1979.
2. Bianco, P.O., Marano, Anthony, Postoloff, Anthony: Cysts of the semilunar cartilage. The New York State Journal of Medicine. 53:2621, 1953.
3. Bonnin, J. Grant: Cysts of the semilunar cartilages of the knee joint. The British Journal of Surgery. 40:558, 1953.
4. Burke et al: A Biochemical Study of Partial and Total Medial Meniscectomy of the Knee. Trans. of 25th O.R.S. p. 91, Feb. 1978.
5. Cross, Mervyn J., Watson, Stuart A.: Cysts and "pseudocysts" of the menisci of the knee joint. The Australian and New Zealand Journal of Surgery. 51(1): 59, 1981.
6. Edmonson, Allen S., Crenshaw, A.H.: Campbell's Operative Orthopaedics. St. Louis, The C.V. Mosby Company, 1980.
7. Ferriter, Pierce J., Nisonson, Barton: The role of arthroscopy in the treatment of lateral meniscal cysts. Arthroscopy: The Journal of Arthroscopic and Related Surgery. 1(2):142, 1985.
8. Flynn, Mark, Kelly, J.P.: Local excision of cyst of lateral meniscus of the knee without recurrence. The Journal of Bone and Joint Surgery. 58B (1): 88, 1976./9. Gallo, Gary A.: Cysts of the semilunar cartilages of the knee, A report of sixteen cases including arthrographic study. The American Journal of Surgery. 116:65, 1968.
10. Helfet, A.J.: Diagnosis and management of internal derangements of the knee joint. Instruc. Course Lect. Am. Acad. Orthop. Surgery. 19:63, 1970.
11. King, E.S.J.: The formation of ganglia and cysts of the menisci of the knee: Observations on the Golgi apparatus. Surgery, Gynecology and Obstetrics. 70:150, 1940.
12. McDermott, L.J.: Development of human knee joint. Arch. Surgery. 46:705, 1943.
13. Ollerenshaw, R.: The development of cysts in connection with the external semilunar cartilages of the knee joint. The British Journal of Surgery. 8:409, 1921.
14. Seedham, B.B., Downson, D., Wright, V.: Functions of the menisci: A preliminary study. The Journal of Bone and Joint Surgery. 56B(2): 381, 1974.
15. Smillie, I.S.: Injuries of the knee joint. London, Churchill Livingstone, 1978./16. Wroblewski, B.M.: Trauma and the cystic meniscus: A review of 500 cases. Injury: The British Journal of Accident Surgery. 4(4): 319, 1973.

THE UNIVERSITY OF TORONTO

MEDICAL BOOKSTORE

Textbooks for all subjects

Comprehensive reference books
and general interest titles.

Complete review manuals in Medicine and Nursing

- Ask for our free catalogue
- free special order service

OPEN: MONDAY — FRIDAY 8.45 am — 6.00 pm
SATURDAY 11.00 am — 5.00 pm

LOCATION: 214 COLLEGE STREET
(COLLEGE & ST. GEORGE)

TEL: 586-7913

Respirology Rounds

A Seventy-One-Year-Old Woman with Acute Epigastric Pain

Dan Poenaru, B.Sc., 8T6
Robert H. Hyland, M.D. FRCS (C)
Donald P. Jones, M.D. FRCS (C)
Robin R. Gray, M.D. FRCS (C)
The Department of Medicine, Surgery and Radiology, The Wellesley Hospital

Acknowledgements

We would like to thank Miss Jean Calder for her excellent graphic work.

Part 1

A 71-year-old white woman presented to the emergency department with a two day history of severe epigastric pain radiating to the chest and back. The pain was colicky, progressively increasing in severity, and associated with three episodes of vomiting during the previous day. There was no change in bowel habit, dyspepsia, shortness of breath, or fest was clear, with reduced chest wall movement and decreased air entry at the left base. There was tenderness in the epigastrium, but abdominal examination was otherwise unremarkable, as was the rest of the physical examination.

Routine hematology apigastric pain radiating to the chest and back. The pain was colicky, progressively increasing in severity, and associated with three episodes of vomiting during the previous day. There was no change in bowel habit, dyspepsia, shortness of breath, or find biochemistry testing was normal, and the electrocardiogram showed normal sinus rhythm with evidence of a previous anterior myocardial infarct. Three views of the abdomen were unremarkable. The chest roentgenogram is shown below.

What is your diagnosis?

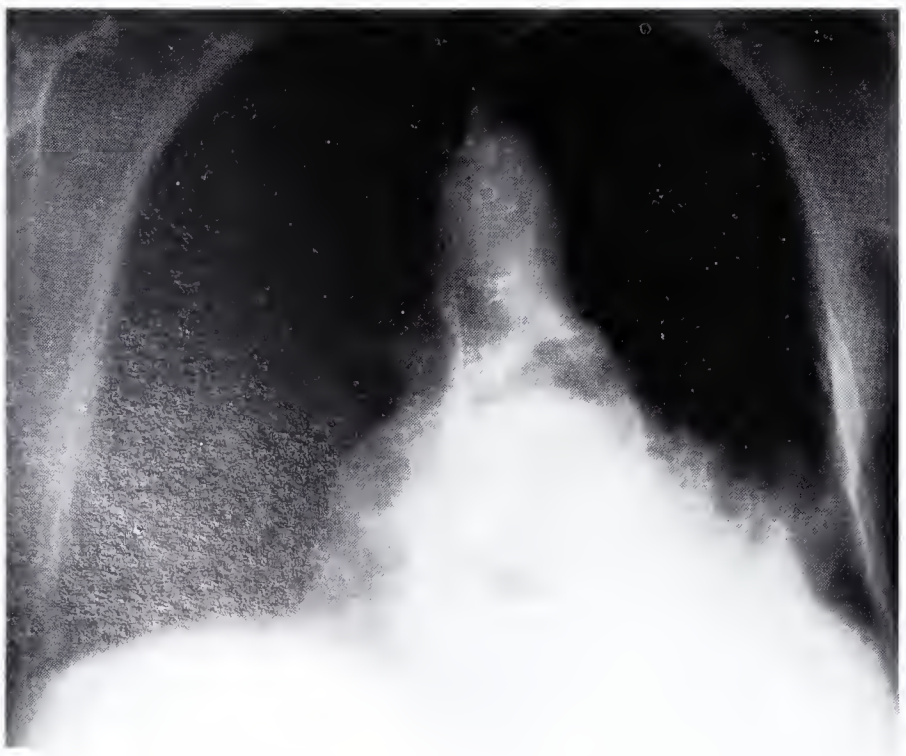


Figure 1 PA Chest A nasogastric tube is present and a mottled air density is seen overlying the heart. The wires are from a previous sternotomy.

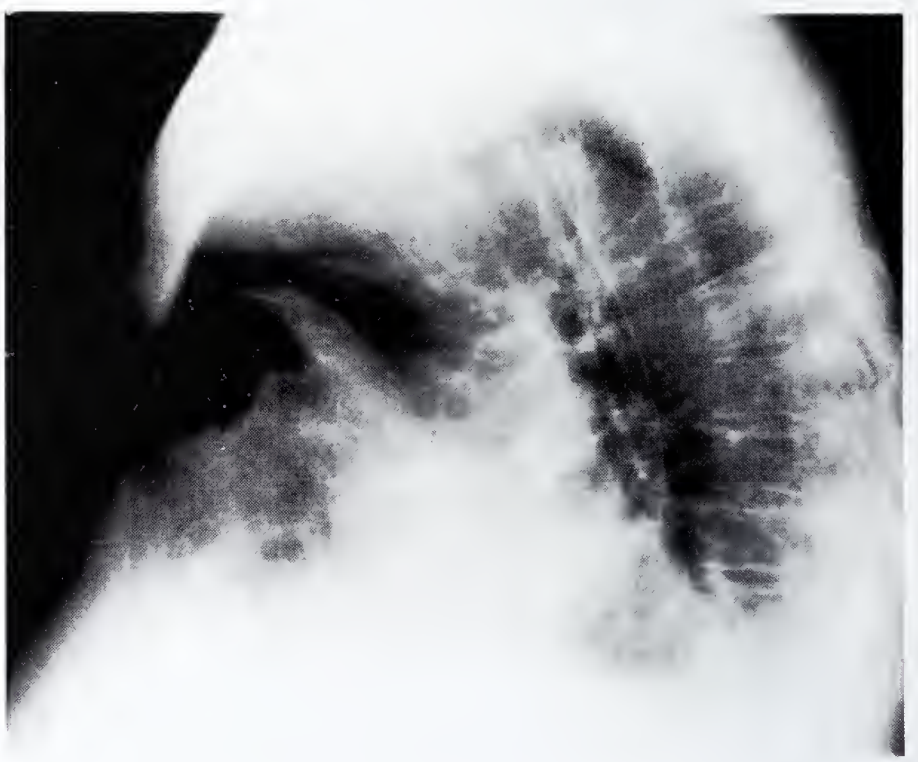


Figure 2 Lateral Chest The nasogastric tube is in the normal position. The mottled density and several collectionsof air are in a substernal location.

Part II

Diagnosis

Incarcerated retrosternal diaphragmatic hernia.

Explanation

The case presented shows the usefulness of a chest film in the investigation of abdominal complaints. PA and lateral views of the chest (Fig. 1, 2) document a segment of bowel in the anterior hemithorax, and hence provide the diagnosis. They Hypaque enema (Fig. 3, 4) identifies the herniated portion as transverse colon, and rules out a perforation.

Course In Hospital

After conservation management with nasogastric suction, intravenous hydration and pain relief, the patient was taken to the operating room where a transabdominal reduction and repair of the hernia was performed. The post-operative course was uneventful, and the patient was discharged home with routine follow-up.

Discussion

Diaphragmatic hernias may be classified as congenital or acquired, and include esophageal hiatus hernias, traumatic hernias, and the congenital foramen of Bochdalek and Morgagni hernias, which may present in infancy or later in life. This brief review will focus on the congenital defects only, with special reference to their presentation during adult life.

A few embryological facts are required to understand the etiology of the various diaphragmatic hernias. During the second month of intra-uterine life, the septum transversum forms caudal to the heart and grows posteriorly to meet the mesentery of the primitive foregut, thus forming the central portion of the diaphragm and separating the peritoneal and pleuropericardial cavities. These cavities remain connected by the paired posterolateral pleuroperitoneal canals, which are later closed by two sets of membranes and buttressed by muscle ingrowth from the cervical myotomes.[1] Failure of union of the various components of the diaphragm can result in potential spaces for internal herniation (Fig. 5).

Esophageal hiatus hernia, which follows the natural defect caused by the foregut crossing the diaphragm, is usually an acquired condition but is increasingly being recognized in neonates.[2] Its symptomatology is directly related to the presence of gastroesophageal reflux, which in infants causes the tetrad of vomiting, respiratory complications, anemia, and failure to thrive.[2]

Persistence of one of the pleuroperitoneal canals — usually the left — leads to the most common type of hernia, the posterolateral hernia of Bochdalek. Escape of the abdominal contents into the thorax results in lung compression, collapse, and mediastinal shift to the opposite side[2] (Fig. 6). The ensuing respiratory distress is usually early and severe, making Bochdalek's hernia a true surgical emergency. However, a few undiagnosed cases survive beyond the neonatal period, to present in later childhood with the aforementioned tetrad.[2]

Finally, the failure of fusion of the sternal and costal elements of the diaphragm can lead to Morgagni's hernia, variously termed retrosternal, parasternal, and subcostosternal hernia. The true etiology of this type of hernia remains unknown. A single embryological defect cannot account for its peak age of diagnosis in the 50's to the 70's, and in fact one theory attributes Morgagni's hernia to mild or severe trauma to the abdominal wall, as well as to the increased intra-abdominal pressure usually resulting from obesity.[3] Alternately, the presence of a hernial sac in the majority of these hernias leads to the suggestion that this may constitute a variant of eventration (i.e., outpouching) of the diaphragm.[4] Regardless of its true etiology, the

Figure 3 AP Film From Barium Enema The splenic flexure of the colon passes through the foramen of Morgagni. The mottled density on the plain films is feces.

Figure 4 Lateral Film From Barium Enema Colon is seen in the substernal region. Note the "neck" where it traverses the hemidiaphragm.

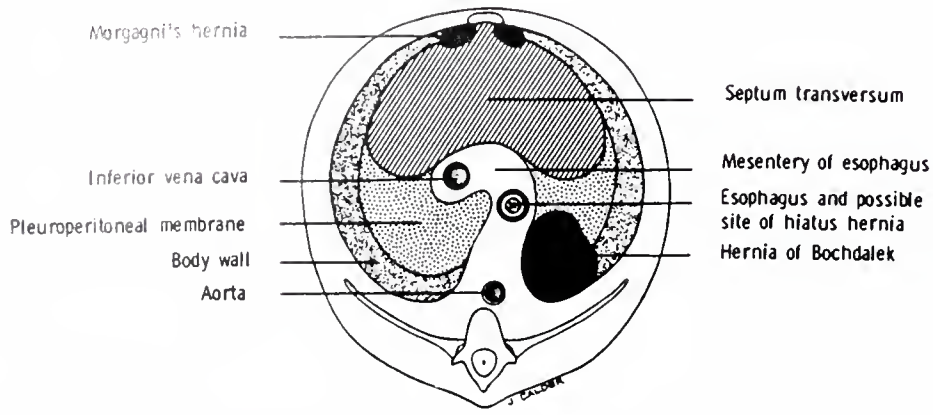


Figure 5 Diagram of a 16 Week Fetus As viewed from below in cross-section, with potential sites for herniation.

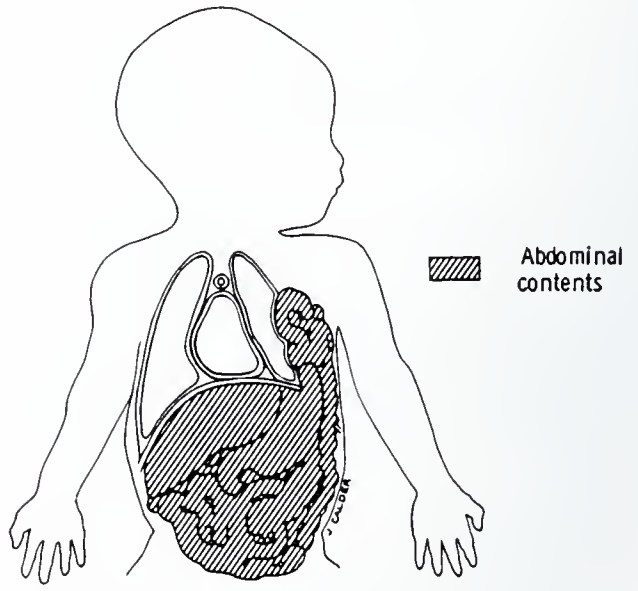


Figure 6 Congenital Diaphragmatic Herniation of Bochdalek Showing abdominal contents compressing the left lung.

defect occurs on either side of the sternum, and usually allows the transverse colon and/or omentum to herniate; portions of the liver and stomach have also been occasionally found in the hernial sac[4]. Morgagni's hernia remains asymptomatic in the majority of patients in which it occurs, presenting as an incidental finding on chest roentgenogram. In the 20% of patients who become symptomatic, vague, nonspecific gastrointestinal complaints make the diagnosis difficult. The more acute picture of severe epigastric pain is usually the result of partial bowel obstruction from strangulation or volvulus of the herniated segment of bowel[5].

While the diagnosis of both Bochdalek and Morgagni hernias can often be made based on chest films alone, contrast studies are indicated when pneumothorax, hydropneumothroax, or lung cysts cannot be excluded.[5]

The management of congenital diaphragmatic hernias varies according to the age of the patient at which the diagnosis is made. Symptomatic posterolateral neonatal hernias require prompt surgical intervention, while hernias of the esophagealiatus in infants should be given an adequate trial of conservative management (upright posture and thickened foods) before surgical correction of the incompetent gastro-esophageal junction is elected. Congenital diaphragmatic hernias in adults, whether symptomatic or not, are often managed surgically in good risk patients, due to the possibility of strangulation. The abdominal approach is simpler and used in most instances; thoracotomy is reserved for cases in which the diagnosis is unclear, as it offers better exposure for other pulmonary, diaphragmatic, or mediastinal conditions[6]. Overall mortality from congenital diaphragmatic hernias is highest in the symptomatic neonatal types (20-40%[7]) and lowest following elective adult surgical repair (3%[8]). Recurrence of Bochdalek and Morgagni hernias after repair is very rare.[1 4] However, patients found to have associated hypoplastic lungs at the time of surgery are likely to be left with residual pulmonary defects.[9]

Conclusion

Congenital diaphragmatic hernias represent a spectrum of abnormalities which are not only encountered by pediatricians. They can present insidiously or acutely during adult life, and a high index of suspicion is required in order not to miss an easily correctable defect.

REFERENCES

1. Oliviera F, Oliviera FJ. Congenital posterolateraql diaphragmatic hernia in the adult. Can J Surg 27(6):610, 1984.
2. Pomerantz M. The diaphragm. In Gibbon's Surgery of the Chest. W.B. Saunders Co., 1983.
3. Boy DP. Diaphragmatic hernia through the foramen of Morgagni. Surg Clin N Am 41:839,1961.
4. Thomas TV. Subcostosternal diaphragmatic hernia. J Thor Cardiovasc Surg 63(2):279, 1971.
5. MacDougall JT, et al. Herniation through congenital diaphragmatic defects in adults. Can J Surg 6:301, 1963.
6. Payne WS, Ellis Jr FH. Esophagus and diaphragmatic hernias. In Principles of Surgery, 4th ed., McGraw-Hill, 1984.
7. Graivier L. Congenital diaphragmatic hernia. South Med J 67(1):59, 1974.
8. Fingerhut A, et al. Deux observations de hernia diaphragmatique postero-lateral congenitale (dite de Bochdalek) revelees a l'age adulte par des complications severes. Intervention et guerison. Revue de lat literature. J Chir (Paris) 115:135, 1978.
9. Saw ES, et al. Congenital posterolateral diaphragmatic hernia in children. Calif Med 119:6, 1973.

A Model Of Pulmonary Hypertension in Dogs

D. Gluckman, J. D. Cooper M.D.

Clinically, chronic pulmonary hypertension may be divided into several categories including primary, embolic, pulmonary venous, and hypoxic pulmonary hypertension, as well as that associated with pulmonary parenchymal disease and unrepaired congenital heart disease. Once established, the obliterative vascular lesions of pulmonary hypertension, and the resulting right ventricular hypertrophy and ultimate failure is almost always fatal [1 2 3]. For patients suffering from pulmonary hypertension unresponsive to vasodilators or other forms of medical treatment, lung or heart-lung transplantation may provide functional improvement and increased longevity.[3 4 5]

The aim of this study is to develop a model of chronic right ventricular hypertrophy and failure in dogs and to then assess the right ventricular structure and function over time when pulmonary vascular resistance (PVR) is restored to baseline values.

Several models of pulmonary hypertension in dogs have been investigated. The pulmonary vasacular bed has been embolized with large amounts of material such as glass beads,[6 7 8] acrylic beads[9], crushed pentazocine tablets,[10 11] suspended barium sulphate [12] sphadex microspheres,[13] clots, polystyrene spheres, lycopodium spores, and silica particles.[7 8 14] While the pentazocine suspension caused a granulomatous reaction with the pulmonary vasculature, most other techniques reported only transient effects and/or an unacceptably high level of morbidity and mortality. Microembolization of small amounts of sephadex microspheres over many months was attempted in this laboratory, but proved to be inefficient and unsuccessful in producing chronic pulmonary hypertension.

A chemical model of lung injury-induced pulmonary hypertension has been studied using monocrotoline, a pyrrolizidine alkaloid found in the seeds of the plant *crotalaria spectabilis*. While it effectively induces progressive pulmonary hypertension in rats, reports of similar results in dogs have been conflicting.[3 14 15]

Several mechanical models have been studied. Previous investigators have used banding of the pulmonary artery [16 17] and distension of the pulmonary artery using a balloon catheter[18 19] These techniques caused a high mortality rate from acute right ventricular failure and only transient pulmonary hypertension respectively. A device consisting of a stainless steel jacket containing a cylinder of hygroscopic casein plastic called Ameroid has been used in various studies involving gradual vascular occlusion.[20-25] Gradual constriction of the left and right pulmonary arteries by Ameroid constrictors successfully induced chronic RV failure in 1 dog in this laboratory; however, reversibility was impossible as the plastic had eroded through the vessel wall and the dog exsanguinated upon removal of the constrictor. Other investigators have reported using a tourniquet system to adjustably band the pulmonary artery of infants with complex congenital cardiac abnormalities.[26] While it is reported to be effective, this method requires a skin incision for adjustment.

A simpler model was selected employing an inflatable silastic balloon 27 placed around the main pulmonary artery, attached to a subcutaneous reservoir. Periodic injection of liquid into the reservoir gradually constricted the balloon, inducing chronic pulmonary hypertension and ultimate chronic RV failure. The development and reversibility of chronic right ventricular failure, and the reversibility of cuff-induced pulmonary artery stenosis are presently being studied.

Methods

Pre-operatively at cuff placement, seven adult mongrel dogs weighing from 22 to 28 kg were each shaved over the thorax, given IM penicillin and all air was removed from the cuffs by repeatedly filling and aspirating the system with saline. The dogs were then anaesthetized with intravenous sodium pentothal (20mg/kg), intubated with an endotracheal tube, and placed left side facing upward. The dogs were ventilated using a positive-pressure respirator and maintained under anaesthesia using 1.5% fluothane. The thorax was entered through the left third intercostal space. The pericardium was opened between and parallel to the left phrenic and vagus nerves, and the main pulmonary artery was isolated. Right ventricular pressure (RVP), and distal pulmonary artery pressure (Ppa) were measured using the direct insertion of a 22-gauge needle attached via pressure transducers to a Hewlett-Packard Multi-Channel Recorder. The silastic balloon was placed around the main pulmonary artery and its ends were sutured together such that there was a minimal increase in systolic Ppa (3mm Hg). The cuff was tested by inflating the balloon with 0.1 ml increments of saline, and RVP and distal Ppa were

W.B. Saunders Company
Canada Limited
WORLD'S LARGEST
HEALTH SCIENCE PUBLISHERS
Distributors for: **Merck Inc., Bailliere Tindall, Igaku-Shoin, Springhouse, Slack Inc.**
One Goldthorne Ave., Toronto, ON. M8Z 5T9
(416) 251-3787
Available through
U of T Medical Bookstore

recorded at each volume. The saline was removed from the cuff and the reservoir was buried sub-pectorally. A marcaine intercostal nerve block was given, the incision was closed, and the dogs were allowed to recover.

A week after surgery the dogs were anaesthetized in a similar manner. After taking a postero-anterior chest x-ray, a Swan-Ganz catheter was introduced into the external jugular vein through a small incision in the upper area of the left neck and was passed into the pulmonary artery. Measurements of RV end-diastolic pressure (RVEDP), Ppa, and pulmonary wedge pressure (Ppw) were obtained using the Hewlett-Packard Multi-Channel recorder. Measurements of cardiac output (CO) were obtained using the thermodilution technique (9520A Cardiac Output Computer American Edwards Laboratory).

Echocardiography was performed using an ATL 4000 SC (ADR) mechanical sector scanner capable of 2-D and M-mode imaging. The dogs were connected to the scanner EKG and imaged using a 3MHz transducer. The imaging windows consisted of right parasternal mid-thorax for the short axis and left parasternal 6-8cm from the sternum in the mid-thorax for the four-chamber. The right and left ventricles, and the interventricular septum were imaged using both these views. Photographs were obtained from frozen images with a Polaroid camera.

The Swan-Ganz catheter was then repositioned in the RV. Starting at Oml, the cuff was inflated with 0.1 ml increments of metrizamide Amipaque, an isotonic radio-opaque dye, and RVP measurements and similar echocardiographic studies were done at each volume. A volume of Amipaque was left in the cuff such that the increase in systolic Ppa 5mm Hg. This procedure was repeated every two weeks.

Following the development of RV failure, this first sample of dogs was sacrificed and their hearts were resected. After dissecting the right and left ventricles (leaving the septum with the left ventricle), RV/LV weight and RV wall thickness was determined, and histologic sections were taken.

Chronic right ventricular failure was similarly induced in a second sample of dogs. Pulmonary stenosis was reversed in these dogs by deflating the cuff and a closed repair of the main pulmonary artery. Similar hemodynamic and echocardiographic measurements were then performed every two weeks. RV/LV weight, RV wall thickness, and histologic sections were measured at the end of the study.

In vitro studies were also performed on the cuffs. The acute pressure-volume relationship of eight intact cuffs was measured by inflating each with 0.1 ml increments of saline, and measuring the pressure within the cuffs at each volume using a 25-gauge needle inserted into the reservoir and attached to the Hewlett-Packard Multi-Channel Recorder. The chronic pressure and volume decay of 5 inflated cuffs were also measured. Each balloon was sutured around a piece of rubber tubing, inflated with 1.5 or 2.0 ml of saline and immersed in a beaker of saline. Volume and pressure in the cuffs were measured every few days.

Results

The in vitro studies yielded both interesting and disappointing results. Three of the eight cuffs developed visible leaks during measurement of the pressure-volume relationship. The remaining five cuffs all demonstrated extremely high inflation pressures (Fig. 2). Cuffs 4 and 5 showed a dramatic acute pressure decay at given volumes without having any visible leaks. The five intact cuffs were used to measure chronic pressure and volume decay. Two of them developed visible leaks within the first 5 days; the other three showed volume decay and one showed pressure decay without any visible leaks (Fig. 3a, b).

All seven dogs survived the banding procedure and five subsequently remained alive. Dog #7 died of chronic RV failure secondary to a possible chronic pleural infection and dog #6 died of post-operative complications following an attempt to replace a leaking cuff. While the balloons were able to raise systolic RVP to moderate degrees at cuff placement (Fig. 4) , their effectiveness decreased at subsequent measurements (Fig 5, 6). During the course of the study, the cuffs in dogs #2, 3, 5, and 6 developed acute leaks in which Amipaque could not be retrieved immediately following injection, and those in dogs #2 and 4 developed chronic leaks in which less Amipaque was retrieved at a given measurement than was injected at the previous measurement. The dogs did not show development of chronic pulmonary hypertension or changes in chest x-ray.

Preliminary echocardiography results in dog #1 are shown in Figs. 8 and 9. While the short axis view of Fig 8a and the four chamber view of Fig. 9a show a normal rounded septum with the balloon non-inflated, the short axis view of Fig. 8b and four-chamber views in Figs. 9b and 9c show the septal flattening of right ventricular pressure overload during acute balloon inflation (Fig. 9c shows more pronounced septal flattening at a higher balloon inflation).

Dogs #1 and #2, each having leaking balloons, were sacrificed. Both dogs showed a marked fibrotic reaction around the cuffs with the formation of a pseudocapsule. The pseudocapsule in dog #1 had a low grade suppurative infection and had caused a marked fixed stenosis of the pulmonary artery lumen. These findings were absent in dog #2.

The results in the working model will be analyzed as indicated in Fig. 7.

Fig. 1 Schematic diagram of cuff

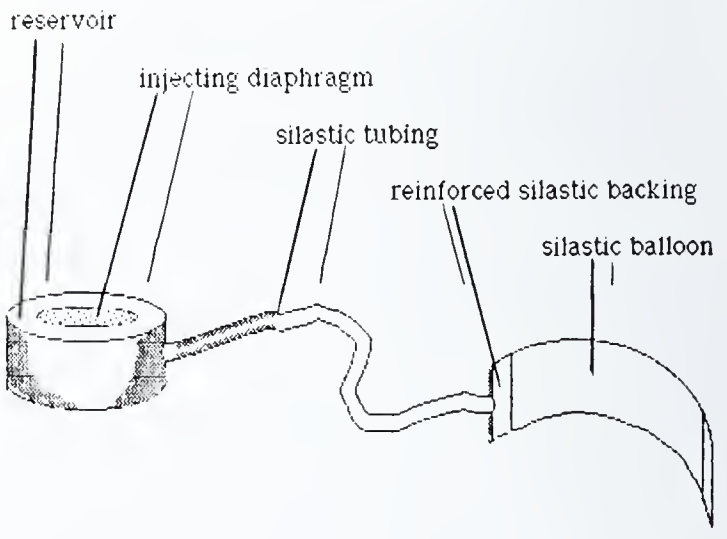


Fig. 2 Acute pressure-volume relationship in vitro

Vol(ml)	Pressure (mmHg)				
	1	2	3	4	5
0.0	15	10	10	20	10
0.1	70	30	50	50	30
0.2	100	50	80	110	60
0.3	150	75	120	180	90
0.4	210	110	160	250	140
0.5	270	160	190	230	200
0.6	310	190	215	170	260
0.7	360	240	250	240	300
0.8	400	285	275	270	290
0.9	>400	310	300	295	305
1.0	"	350	320	260	320
1.1	"	390	340	250	305
1.2	"	>400	360	270	250
1.3	"	"	380	300	250
1.4	"	"	400	300	280
1.5	"	"	>400	210	300
1.6					190
1.7					220
1.8					210
1.9					230
2.0					175

Fig. 4 Systolic RVP at acute cuff inflation cuff placement

Vol(ml)	Pressure(mmHg)								
	1	2	3	4	5	6	7	mean	S.D
0.0	20	24	16	16	30	22	30	23	5.9
0.1	20	28	16	14	30	22	32	23	7.0
0.2	20	26	17	18	32	26	32	24	6.3
0.3	20	22	16	20	34	26	44	26	9.8
0.4	24	26	16	21	36	28	46	28	10
0.5	26	30	16	22	36	24	46	29	9.9
0.6	24	32	17	24	40	30	46	30	10
0.7	36	30	18	23	46	32	48	33	11
0.8	40	31	18	23	48	44	44	35	12
0.9	32	20*	19	24	48	46	26	33	12
1.0	32	38	20	28	50	50	22	34	12

*Swan Ganz Catheter subsequently flushed

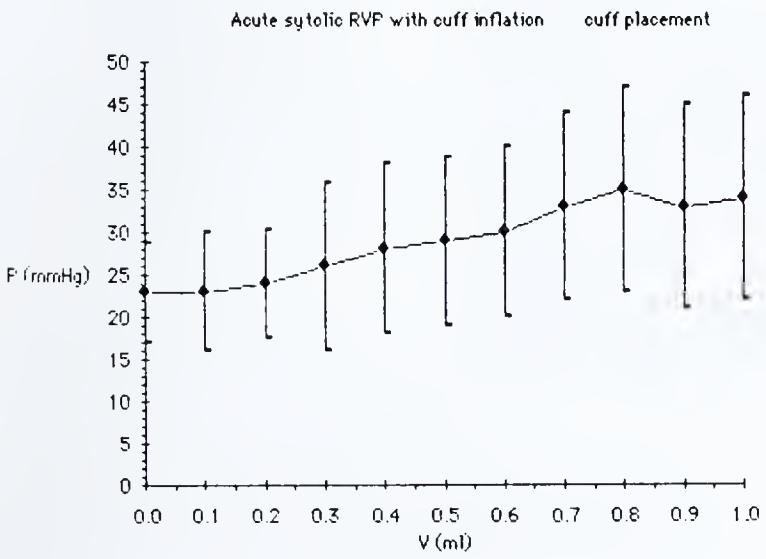


Fig. 3a Chronic volume decay of inflated cuffs in vitro

Day	Volume(ml)				
	1	2	3	4*	5
0	1.5	1.5	1.5	1.5	2.0
2	1.1	1.3	leak	0.5	1.6
5	1.0	1.2		.2	leak

Fig. 3b Chronic pressure decay of inflated cuffs in vitro

Day	Pressure(mmHg)				
	1	2	3	4*	5
0	>400	>400	>400	210	175
2	>400	>400	leak	100	175
5	>400	>400		50	leak

*No visible leak

Fig. 5 Systolic RVP with acute inflation 1st measurement

Vol(ml)	Pressure(mmHg)								
	1	2	3	4	5	6	7	mean	SD
0.0	24	28	16	19	30	32	18	25	6.3
0.1	24	28	16	19	30	33	18	25	6.6
0.2	26	29	16	20	30	34	19	26	6.7
0.3	27	30	16	20	30	32	19	26	6.4
0.4	29	31	17	20	32	30	19	27	6.4
0.5	29	32	17	18	32	28	18	26	6.8
0.6	32	33	17	17	32	34	18	28	8.2
0.7	34	34	18	16	33	30	16	28	8.3
0.8	34	34	18	18	33	-	-	27	8.6
0.9	36	35	18	19	34	31	-	29	8.2
1.0	38	36	18	20	34	28	-	29	8.5
1.1	39	36	19	18	35	-	-	29	10
1.2	41	37	19	17	36	-	-	30	11
1.3	-	38	19	8*	35	-	-	31	10
1.4	-	38	19	14*	36	-	-	31	10
1.5	-	39	20	22	36	28	-	29	8.4

*Swan Ganz catheter subsequently flushed

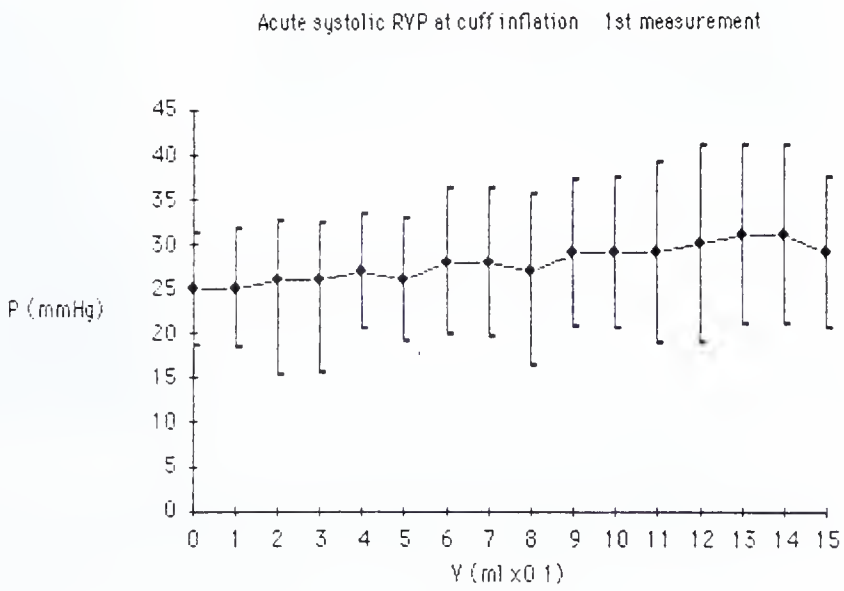


Fig. 6 Systolic RVP at acute cuff inflation
2nd measurement

Vol (ml)	Pressure(mmHg)						
	1	2	3	4	5	6*	7*
0.5	10						
0.6							
0.7	13						
0.8	14	24	29				
0.9	14	24					
1.0	14	22	30	36			
1.1	14	25					
1.2	14	26	30				
1.3	15	25	30				
1.4	15	25	31				
1.5	16	20	30	36	32		
1.6		20	31				
1.7		20		36	36		
1.8		25	29				
1.9		22			36		
2.0		24	30				
2.1		20			36		
2.2			29				
2.3					38		
2.4			29				
2.5					37		
2.6		30	28				
2.7					37		
2.8							
2.9					37		
3.0							
3.1		30			36		
3.2							
3.3					37		
3.4							
3.5							
3.6			30				
3.7							
3.8					32		

*Died before measurement #2

Fig. 7 Analysis of results in the working model

Assess	Measure	Statistic
Pulmonary hypertension	Hemodynamics	
	-RVP(mean, systolic)	paired t
	-RVP-distal PAP gradient across inflated cuff (mean, systolic)	paired t
	?Doppler	
Right ventricular hypertrophy	Echocardiography	
	-RV free wall thickness	paired t
	Pathology	
	-Histology	
	-Heart wt./ Body wt.	t
	-RV/LV wt.	t
	-RV free wall thickness	t
Right ventricular function	Hemodynamics	
	-RVEDP	paired t
	-C.O.	paired t
	Echocardiography	
	-RV end-diastolic dimension (linear, area)	paired t
	-RV motion	qualitative
	-Interventricular septal motion	qualitative
	?Doppler	
	?Nuclear Angiography	
Reversibility of stenosis	RVP-distal PAP gradient across 0ml cuff inflation (mean, systolic)	paired t

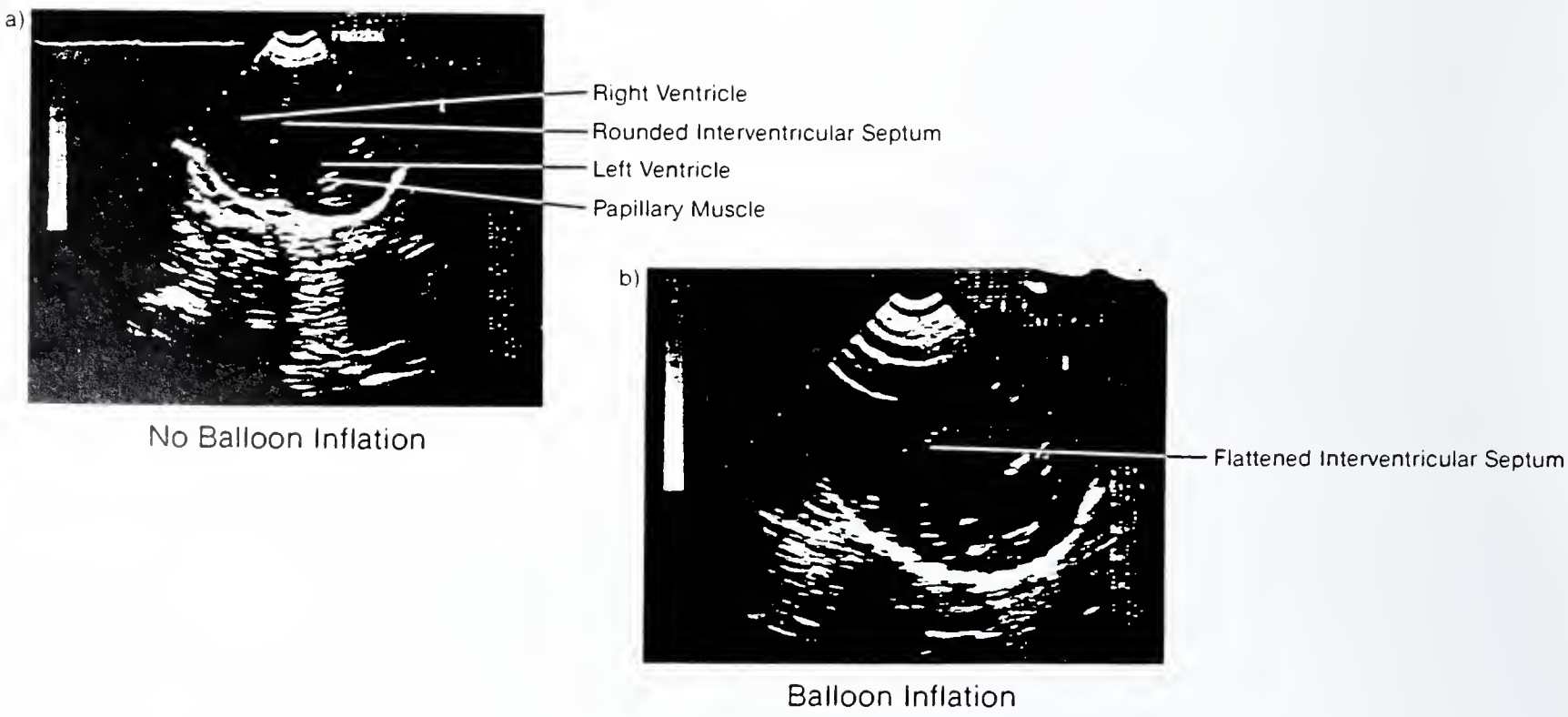


Fig. 8 Short Axis View

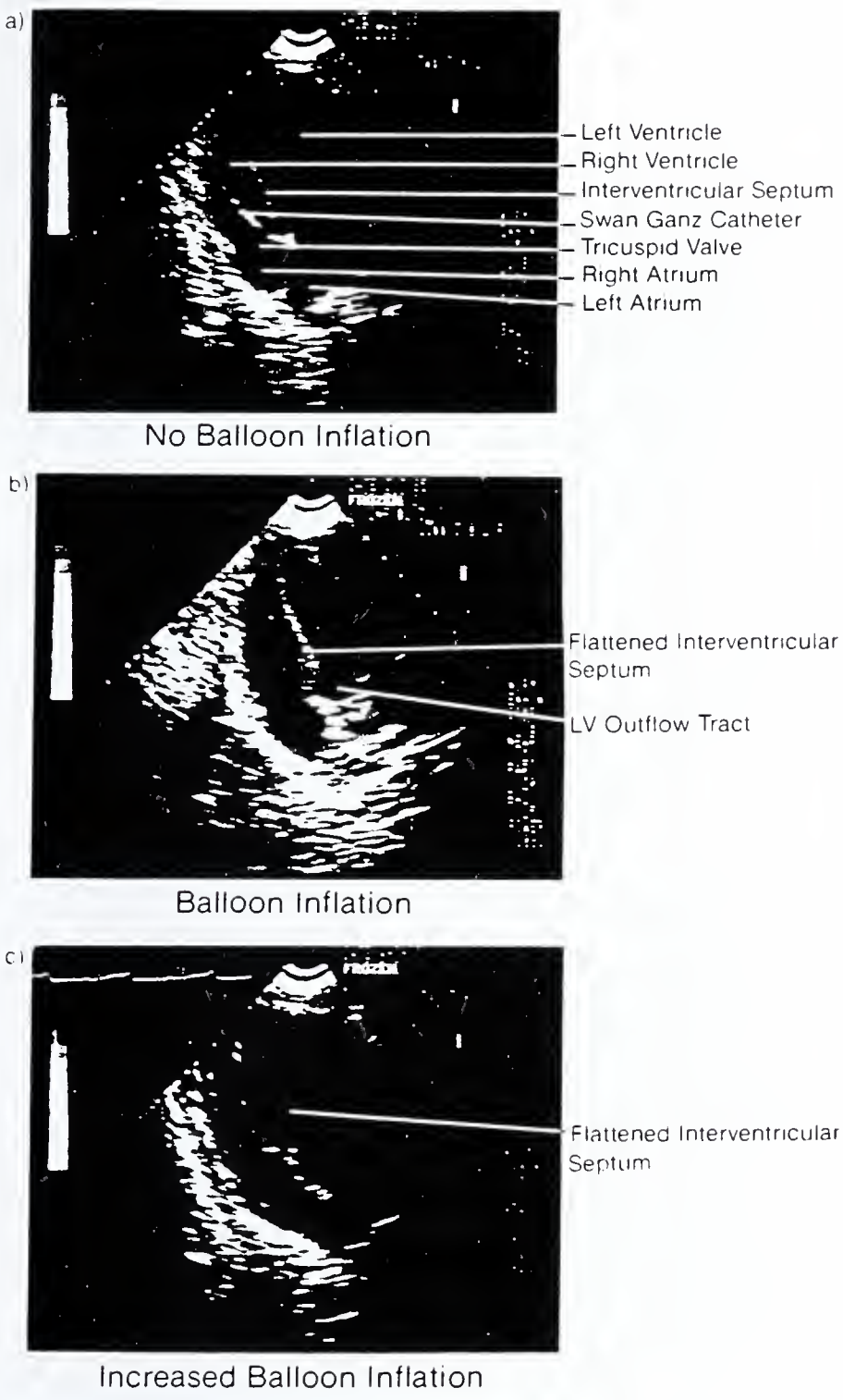


Fig.9 Four Chamber View

Discussion

The inflatable cuff was selected because it offers several advantages. It is an extremely simple device that potentially can effectively cause right ventricular hypertrophy and failure in response to an increasing stenosis of the main pulmonary artery. Mechanical obstruction of smaller pulmonary vessels is less effective as it causes significant changes in hemodynamics only after the area of the vascular bed has been decreased by 50-65%.[1 7 28 29] There are two reasons for this accomodating effect. First, compliant, thin-walled arteries and veins prominent in the pulmonary vasculature can accomodate two to threefold increases in blood volume with only a 1-2mm Hg increase in pulmonary artery pressure. After this point small increments in volume produce relatively large increases in pulmonary artery pressure.[7 30-32] Second, the recruitment of additional pulmonary vessels minimizes the pressure changes in the pulmonary vasculature after vascular obstruction.[7 33]

The controlled gradually increasing stenosis simulates the slow development of right ventricular hypertrophy and failure of human chronic pulmonary hypertension. While no investigators have reported an effective model of chronic right ventricular failure in dogs, the cuffs should permit the development of this condition in this species whose right ventricle is extremely sensitive to pressure changes. Having witnessed in this laboratory the morbidity and mortality of dogs in acute right ventricular failure often following a fairly small rise in pulmonary artery pressure, we incrementally inflate the balloon such that the increase in pulmonary artery pressure is less than 5mmHg. Pulmonary vascular resistance in dogs with chronic right ventricular failure will be restored by deflating the balloons, and a closed repair of the pulmonary artery following dissection of the fibrotic pseudocapsule then follows.

The hemodynamic studies show the potential for effective controlled development of pulmonary hypertension and ultimate right ventricular failure (Fig. 4). The initial echocardiographic studies show that effective imaging of the dog heart is possible, and demonstrate the effectiveness of the balloons in inducing right ventricular overload. However, leakage of the cuffs and the small volume of the balloons still present problems. Several solutions may be pursued. The qualtiy of seals of these cuffs can be improved and similar balloons of larger volume can be used. A new constricting apparatus can also be designed. High volume-low pressure balloons having less tendency to leak may be constructed using alternate materials such as latex or polyvinylchloride. Seamless spherical balloons having an optimal internal pressure distribution may be designed instead of the present cylindrical balloons having an unequal pressure distribution. Although more awkward, an extrathoracically adjustable tourniquet system[26] can also be employed.

Improvements in the model for the next stage will include:

More effective stenosis:
- larger balloons

Less leakage:
- reinforced silastic balloons with stainless steel reservoiirs are being tested at the Mayo Clinic
- balloons pre-tested by the manufacturer to withstand 1500mmHg pressure
- avoid over-inflation of the balloons by determining their maximum volume (the volume necessary to inflate the balloons to 1500 mmHg pressure)
- bench test all balloons for acute and chronic leakage before placing them into dogs
- avoid piercing the reservoir by injecting the cuffs with a 25-gauge needle at exactly a 90 degree angle in the center of the diaphragm
- with the dogs sedated refill the balloons to previously inflated volume once per week (in present protocol, balloons are inflated to new volume once per 2 weeks)

Decrease amount of peri-cuff infection and fibrosis:
- broad spectrum antibiotic coverage pre- and post-operatively

The percutaneously adjustable pulmonary artery band permits the simple effective investigation of the pathophysiology of the right ventricle in chronic pulmonary hypertension. Investigation of the potential reversibility of right ventricular failure will indicate whether lung transplantation or heart-lung transplantation should be performed as a treatment for chronic pulmonary hypertension refractory to other forms of therapy. The device also promises importance in the treatment of various complex congenital cardiac abnormalities.

REFERENCES

1. Wagenvoort C.A., Wagenvoort N. Pathology of pulmonary hypertension. John Wiley & Sons, Inc., New York. 1977.
2. Hatano S., Strasser T. Primary Pulmonary Hypertension, Report on a WHO Meeting. World Health Organization. 1975.
3. Weir E.K., Reeves J.T. Pulmonary Hypertension. Futura Publishing Company, Inc., New York. 1984.
4. Reitz B.A., Wallwork J.L., Hunt S.A., Pennock J.L., Billingham M.E., Oyer P.E., Stinson E.B., Shumway N.E. Heart-Lung Transplantation: Successful Therapy for Patients with Pulmonary Vascular Disease. NEJM 306(10): 557-564, MAR 11 1982.
5. Jamieson S.W., Stinson E.B., Oyer P.E., Theodore J., Hunt S., Dawkins K., Billingham M., Shumway N.E. Heart and Lung Transplantation for Pulmonary Hypertension. Am. J. Surg. 147(6): 740-742, Jun 1984.
6. Weedn R.J., Guenter C.A., Greenfield L.J. Effects of Pulmonary allotransplantation in dogs with microembolic pulmonary hypertension. An. Thor. Surg. 13: 181-187, 1972.
7. Malik A.B. Pulmonary Microembolism. Phys. Rev. 63: 1114-1207, 1983.
8. Hyland J.W., Smith G.T., McGuire L.B., Harrison, D.C., Haynes F.W., Dexter L. Effect of selectivie embolization of various sized pulmonary arteries in dogs. Am. J. Physiol. 204: 619-625, 1963.
9. Coalson J.J., Kastl D.G., Whale M.H., Greenfield L.G. Allografted lungs in matched dogs with induced pulmonary hypertension. Am. J. Path. 74: 533-543, 1974.
10. Farber H.W., Falls R., Glauser F.L. Transient Pulmonary Hypertension from the intravenous injection of crushed pentazocine tablets. Chest 80: 178-182, 1981.
11. Arnett E.N., Battle W.E., Russo J.V., Roberts W.C. Intravenous injection of talc-containing drugs intended for oral use. Am. J. Med. 60: 711-718, 1976.
12. Saleh S.S., Hardy J.D. Lung transplantation for the treatment of pulmonary hypertension in dogs. Arch. Surg. 96: 340-343, 1968.
13. Shelub I., van Grondelle A., McCullough R., Hofmeister S., Reeves J.T. A model of embolic chronic pulmonary hypertension in the dog. J. Appl. Physiol. 56(3): 810-815, 1984.
14. Shumway N.E., Larson D.F., Womble J.R., Copeland J.G., Russell D.H. Concurrent left and right ventricular hypertrophy in dog models of right ventricular overload. J. Thoreac. Cardiovasc. Surg. 84: 543-547, 1982.
15. Olson J.W., Hacker A.D., Altiere R.J., Gillespie M.N. Polyamines and the development of monocrotaline-induced pulmonary hypertension. Am. J. Physiol. 247(4Pt.2): H682-685, Oct. 1984.
16. Sarwat A.K., Fonkalsrud E.W., Chappel G. Lung Allotransplantation in dogs with pulmonary hypertension. Surg Forum 23: 229-231, 1972.
17. Fjonkalsrud E.W., Sarwat A.K., Higashijima I., Sanchez M., Chappel G. Lung allotransportation in dogs with pulmonary hypertension. Arch. Surg. 106: 785-787, 1973.
18. Juratsch C.E., Jengo J.A., Castagna J., Laks M.M. Experimental pulmonary hypertension produced by surgical and chemical denervation of the pulmonary vasculature. Chest 77: 525-530, 1980.
19. Juratsch C.E., Jengo J.A., Laks M.M. Role of the Autonomic Nervous System and Pulmonary Artery Receptors in Production of Experimental Pulmonary Hypertension. Chest 7 1(2 suppl.): 265-269, Feb. 1977.
20. Huang C.L., Norico A.P., Baker R.R. Changes in pulmonary blood flow produced by autotransplantation of the left lung and placementy of an Ameroid constrictor on the right pulmonary artery. J. Cardiovasc. and Thor. Surg. 62: 131-137, 1971.
21. Hammond G.L., Provan J.L., Austen W.G. Experimental Evaluation of Myocardial Revascularization Procedures. An. Surg. 164: 951-958, 1966.
22. Provan J.L., Hammond G.L., Austen W.G. Flowmeter studies of internal mammary artery function after implantation into the left ventricular myocardium. J. Thor. Cardiovasc. Surg. 52: 820-828, 1966.
23. Vineberg A., Mahanti B., Litvak J. Experimental gradual coronary artery constriction by ameroid constrictors. Surgery 47: 765-771, 1960.
24. Litvak J., Siderides L.E., Vineberg A.M. The experimental production of coronary artery insuffiency and occlusion. Am. Heart J. 53: 505-518, 1957.
25. Duchesne E.R., Vineberg A. An experimental study of the effect of mechanically induced ischemia upon the coronary anastomoses. Surgery 43: 837-848, 1958.
26. Muruaka R., Yokota M., Aoshima M., Nomoto S., Kyoku I., Kobayashi A., Nakano H., Ueda K., Saito A. Extrathoracically adjustable pulmonary artery banding. J. Thorac. Cardiovasc. Surg. 86: 582-586, 1983.
27. Solis E., Heck C.F., Seward J.B., Kaye M.P. Percutaneously adjustable pulmonary artery band?
28. Berman J.K., Fields D.C., Judy, Hubert, Mori, Victor, and Parker, Roland J. Gradual vascular occlusion. Surgery 39: 399, 1956.
29. Dalen J.E., Haynes F.W., Hoppin F.G., Evans G.L., Bhardwaj P., Dexter L. Cardiovascular responses to experimental pulmonary embolism. Am. J. Cardiol. 20: 3-9, 1967.
30. Fishman A.P. Dynamics of the pulmonary circulation. In: Handbook of Physiology. Circulation, edited by W.F. Hamilton and P. Dow. Washington, DC: Am Physiol. Soc. 2: 1667-1743, 1963.
31. Lategola M.T. Pressure-flow relatiionships in the dog during acute, subtotal pulmonary vascular occlusion. Am. J. Physiol. 192; 613-619, 1958.
32. Lategola M.T., Rahn H. Studies in Respiratory Physiology (2nd Ser.) Dayton, OH: Wright Air Dev. Center, p. 180, 1955.
33. Permutt S., Caldini P., Maseri A., Palmer W.H., Sasamori T., Zierles K. Recruitment versus distensibility in the pulmonary vascular bed. In: The Pulmonary Circulation and Interstitial Space, edited by A.P. Fishman and H.H. Hecht. Chicago, IL: Univ. of Chicago Press, P. 375-390, 1969.

Canadian Midwifery Reborn

Vivian Rushworth, 8T7

Introduction: In the seventies, the movement of midwifery was initiated by people felt dissatisfied with available perinatal care. Midwifery reappeared to meet the community demands for less unnecessary medical intervention, and more respect, sensitivity and caring in birth attedants. This movement has exploded with the support of satisfied consumers and concerned health professionals. Midwifery in Ontario today is now under review by the Health Professions Legislative Review Committee and is likely to be incorporated into the present health care system in the not too distant future. The return of midwifery to Canada starts with an answer to the oft asked question, "What is a midwife?"

What is a Midwife?

The World Health Organization uses the definition developed by the International Confederation of Midwives and the International Federation of Gynaecology and Obstetrics

> A midwife is a person who, having been regularly admitted to a midwifery educational programme, duly recognized in the country in which it is located, has successfully completed the prescribed course of studies in midwifery and has acquired the requisite qualifications to be registered and/or legally licensed to practice midwifery.
>
> The sphere of practice: She must be able to give the necessary supervision, care and advice to women during pregnancy, labour, and the post-partum period, conduct deliveries on her own responsibility and to care for the newborn and infant. This care includes preventative measures, the detection of abnormal conditions in mother and child, the procurement of medical assistance and the execution of emergency measures in the absence of medical help.
>
> She has an important task in health counselling and education not only for patients but also within the family and community. The work should involve ante-natal education and preparation for parenthood and extends to certain areas of gynaecology, family planning and child care. She may practice in hospitals, clinics, health units, domiciliary conditions or any other service.

In Canada, there are no schools of midwifery or provisions for licensing and regulating midwives. Consequently, three different types of midwives exist today. These are: 1) the direct-entry midwife, foreign trained in a recognized program usually lasting three years with no nursing background, 2) the nurse-midwife, foreign trained with a combined diploma of nursing and midwifery, and 3) the lay midwife, who is self-trained, usually apprenticed to an experienced midwife and/or physician and who has no formal diploma.

With the present lack of legal status, anyone can conceivably call themselves a midwife and carry on a practice as such. Everyone involved with maternity care would like to see this changed. The Midwives Coalition, a joint committee of the AOM (Association of Ontario Midwives) and the MTF (Midwifery Task Force) has been requested to submit recommendations for education and self-regulation to the HPLRC. The Coaliltion hopes that the imminent legalization ofmidwifery will put these recommendations into practice, thus ensuring the high quality of midwifery practiced in Ontario.

The Decline of Midwifery in Canada

Up until the mid-nineteenth century, midwifery thrived in all parts of Canada. Doctors did not attend births. In the 1850's members of the male-dominated medical profession began to encroach on the midwife's practice in order to supplement their incomes. A large-scale campaign was begun by doctors seeking to eliminate their economic competitors. A similar movement was afoot in the United States.[1] [2] [3] In her book, *"Midwifery is Catching"*, Eleanor Barrington quotes a letter to the Canada Lancet of 1873 which admits that deliveries are "to many of us country doctors a very renumerative part of our practice" and that they disliked losing income to "old bodies and quacks".[4]

The attempt to eliminate midwifery was not based on careful health care planning or with the intent to improve the quality of maternity care. On the contrary, with the movement of births into hospitals, the quality of maternity care plummeted.[5] Women started dying from puerperal infections spread by unwashed medical hands. One study in 1930 showed that hospital births resulted in maternal mortality of 5.3 per 1000 while home births had 2.3 per 1000.[6] Forceps deliveries became commonplace, setting the trend of medical intervention in normal labour and birth. In 1885 the Canada Lancet comments, "At the present state of advance (in forceps use) we shall soon overtake Nature and relegate Her to a back place."[4] Midwives continued to lose ground as legislation was brought into effect prohibiting them from practicing in hospitals.

With the introduction of improved sanitation, drugs, and blood transfusions in hospitals, the maternal morbidity and mortality statistics improved. Perinatal care in other countries was improving at the same time, but the countries

Compliments of

AT THE SERVICE OF CANADIAN MEDICINE
AND PHARMACY FOR OVER FIFTY YEARS

SCHERING CANADA INC.
3535 Trans-Canada, Pointe Claire (Québec) H9R 1B4

with the most rapid and significant improvements have been those with systems based on midwifery.[1 7 8 9 10] The legal practice of midwifery in Canada was officially ended in 1947 when the Canadian Medical Association made labour and birth solely a physician's responsibility. Today, of 210 World Health Organization countries, Canada is the only industrial country, along with 8 third world countries in which midwifery is not legally recognized.

Misconceptions

It is a classic debating ploy in intentionally misinterpret an opponent's position and then argue against that altered position. This is what medicine has done in its propaganda campaign against midwifery. The image of the midwife has been so twisted by some members of the medical profession that the public has, for many years, been disinclined to investigate further. This twisted image extends to include the midwife's clients, thus discrediting the opinions of those who have benefitted from the practice of midwifery. The new midwives occupy, hence, a difficult position, tenuously perched on the thin edge of the wedge demanding charge in maternity care.

One image that has permeated a large proportion of the public view is that of midwives and their clients being a minority fringe of "hippie-radical-lunatic back-to-mother-earth-alternate-lifestyle granola grannies". Every movement against an established system has its supporters who are motivated mainly by rebellion instead of by the commitments of the movement. In the midwifery movement, these are the people who deliver into hot tubs, follow prenatal diets taken from the back of a bulghar wheat cereal box, exchange recipes for placenta soup, refuse medicare care of any kind fearing that it will interfere with their spiritual experience, and are ungrateful and even hostile towards medical intervention when they are forced to seek help. These are not representative samples of the Canadian midwifery movement, although they are often held to be by those to seeking to strengthen the argument against midwifery. Most midwives currently practicing in Ontario insist that their clients see a physician throughout the prenatal period. They also ask their clients to ensure that their doctors will agree to provide emergency backup at the hospital.

Midwives are incorrectly associated with home births. Holliday Tyson, a Toronto midwife, speaking on behalf of her colleagues, stated that they are definitely not advocates of home births without medical backup. Home births are not without risks, and no midwife will argue that point. But one must also be aware that hospital births are not without significant iatrogenic and psychological risks to both the mother and the child. Unfortunately, the best system, in which midwifery and medicine operate together as a team, has yet to be established in Canada. Until it is, consumers have a right to choose a system they feel is an improvement over the existing one. Until midwives receive the status allowing them to practice in hospitals or birthing centers, they will continue to attend home births for people who have researched and weighed the alternative risks.

Another misconception is that nursing and midwifery are similar professions. Although a number of midwives are nurses as well, nursing skills are not prerequisites for midwifery. The medical profession itself, in claiming that midwives are practicing medicine, supplies evidence that midwifery is distinct from nursing. One could even argue that if doctors feel that midwives are indeed practicing medicine, and that moreover insist that a year or two of nursing should be a prerequisite for midwifery, then nursing itself should be prerequisite to medicine? Why should midwives have to be nurses first if doctors are not? It is important to realize that the three professions are vastly different, because this will have a bearing on the type of midwifery training established in Ontario. There is one proposal before the HPLRC to institute midwifery training through the College of Nurses of Ontario rather than initially establishing an independent College of Midwives. A year of nursing may or may not be required in this proposal. If this is instituted, the quality of midwifery may suffer. We would not truly have an alternate choice for maternity care if midwives are closely associated with a profession that is still struggling to shake the role of "handmaiden" to the physician. Medicine has traditionally held an authoritative position over nursing and unfortunately still does today in spite of valiant efforts by many nurses to break the shackles. If medicine is given power over midwifery throughout the College of Nurses of Ontario, it will be difficult to maintain the non-interventionist, supportive model of midwifery as it exists today. It is likely that under medical supervision, midwifery students will be compelled to adopt the practices of the very system that necessitated their revival.

It must be emphasized, that although the medical profession in general is responsible for the propaganda against midwifery, many individual physicians recognise the value of midwifery and support the current movement to incorporate it into the present health care system. Dr. Robert Willson, a professor in the obstetrics/gyneacology department at the University of New Mexico School of Medicine states, "An ideal arrangement would be a team of obstetricians and nurse-midwives who share obstetric care, the nurse-midwife being principally responsible for patient education and counselling, which we physicians generally do not do well, and for prenatal, delivery, and postnatal care for normal patients. The obstetrician would serve as a consultant and devote most of his or her time to patients who need the skills of the specialist".[11]

One final and rather interesting misconception is that midwifery is a radical alternate form of maternity care. On the contrary, "modern obstetrics" is actually the radical alternative. It was introduced in the early 1900's, and has not proven to be a success for low risk pregnancies. Public opinion is now swinging back to the centuries old, tried and true, traditional method of birth: with a midwife.

The Issue of Safety

When the issue of safety arises, it is usually only the physical risk factors inherent in childbirth that are considered. There are, in fact, three separate areas of risk; physical, psychological, and iatrogenic. All are intermixed, but the latter two are ignored in the practice of modern obstetrics.

Medical care today is to be commanded on the advances made in reducing mortality and morbidity. High risk pregnancies, which in the past had tragic outcomes, now result in healthy babies and mothers. Most pregnancies (85-90%) though, resolve normally and naturally without the need for intervention. The practice now is to apply many of the medical techniques used for high risk pregnancies to normal pregnancies as well. The rationale for this is the prevention of possible complications. The decision of whether or not to intervene is also influenced by the ever-increasing threat of malpractice. By following this regime of "just-in-case" obstetrics, many members of the medical profession have introduced new risks that outweigh the potential risks of normal labour and delivery. Dr. Caldero Barcia, former head of the International Confederation of Gynaecology & Obstetrics, goes so far as to state that "iatrogenia is the main cause of fetal distress."[12]

In choosing to deliver in the hospital, the low risk mother exposes herself to risks of which she may not be aware. A seemingly innocuous intervention, such as keeping the labouring woman NPO (nothing by mouth) in case she needs a section, can result in a chain reaction of complications and traumas. After fourteen hours of labour without nourishment she is exhausted and becomes a candidate for forceps, oxytoxin, or a caesarian section.

Epidurals are used for 80% of the patients in Toronto. Incorrectly administered, they will either not work or end up as spinal anesthetics. They involve the risk of hypotension with resultant maternal and fetal anoxia. Since the sensation to push is dulled, progress is often arrested with the head in midpelvis. Fetal distress ensues, and forceps are used, with all their inherent risks to the fetal cerebrum, facial nerve, brachial plexus, and birth canal structures.

A labouring woman is not monitored continously in the hospital as there is not enough nursing staff available. A nurse will initially check in on her every half hour and more frequently as she progresses. The woman and her partner, who is often more frightened than she, are left alone between checks. The increased anxiety magnifies the pain of contractions, makes rest between contractions difficult, and tenses muscles which hinder descent. Labour is prolonged in many cases and the woman may again become a candidate for forceps, oxytoxin, or a C-section. Also, minor problems easily dealt with at an early stage progress to serious complications in the unattended woman. The use of fetal monitors is not a substitute for trained attendants.[18] [19] [20]. The midwife, staying at the bedside throughout the entire labour, detects complications as they occur, and is a familiar face, a better judge of the progress and the reserves of the mother and a continuous source of information, reassurance and encouragement for the labouring woman.

It is not uncommon for the woman to deliver before the doctor arrives. Luckily, most hospitals prefer to hire nurse-midwives for their obstetrical floors.

Narcotics are substituted for emotional support and result in a depressed baby and groggy mother. Most women object to the bland reassurances that it is alright if their baby is "a little depressed" since the hospital is equipped with resuscitation equipment and skilled personnel.

Hospital-acquired infections occur even on post-partum wards. Infection of an episiotomy or an umbilical cord by a highly resistant organism can have serious consequences.

Psychological effects are produced by the interruption of bonding and breastfeeding after delivering a narcotized child, by having the child taken from the mother to be observed for twenty-four hours in the nursery following a c-section, and by hospital routines where rooming-in is not allowed. These insidious and intangible psychological traumas are often shrugged off by doctors as being of no immediate consequence. The effects are long-term though, and have heartbreaking consequences in later life. The lack of the special bonding time directly following a birth is associated with a higher incidence of child abuse, neglect and failure to thrive.[13]

Many women are quite happy with their hospital births. They may be the lucky ones who have found non-interventionist physicians. Alternatively, they may be victims of the propaganda against midwives and are not aware of the risks of modern obstetrics. They may also not be aware that there are alternatives and that they are within their rights to choose these alternatives.

Other women, while taking into account the lack of emergency medical backup, still choose home birth attended by a midwife as being safer than modern obstetrics. Anyone interested in the debate surrounding the safest methods for childbirth should be referred to David Stewart's book, *The Five Standards of Safe Childbearing*. Stewart lists numerous international studies on morbidities and mortalities associated with birth. The best results come from those systems with the largest proportion of midwives.

Our study is particularly interesting as it compares the performances of the three groups of maternity care givers: obstetricians, general practitioners, and midwives. In Madera County, California, perinatal care was conducted solely by general practitioners prior to 1960. The population consisted mainly of low income farm workers who were considered higher risk than the average population. Statistics in 1959 showed a neonatal mortality rate of 2.39% and a prematurity rate of 11.0%. From 1960 to 1963 a nurse-midwifery program was run at the Madera County Hospital. During this time, neonatal mortality rates dropped to 1.3% and prematurity rates to 6.4%. In 1963, nurse-midwives were replaced by obstetricians. The results were startling. From 1964 to 1966, neonatal deaths tripled, even surpassing the results obtained by general practitioners. The rates of premature births almost doubled, reaching 9.8%.[14] [15]

Another set of statistics from the North Central Bronx Hospital in New York is equallyl remarkable.16 The North Central Bronx is located in a socio-economically depressed area of New York City. More than 30% of the maternity patients definitely fall into the high risk category. Due to difficulties in obtaining a sufficient number of obstetrical staff members, the hospital decided to put midwives in charge of obstetrical care and used doctors only for appropriate medical consultation. The management of care is summarized as follows:

allowed to eat and drink and encouraged to walk around during labour	100%
delivered in labour bed (not transferred to delivery table)	85%
use of ARMs, elective inductions	0%
use of oxytocin	3%
delivered in semi-sitting position rather than supine lithotomy	85%
use of forceps	2.3%
analgesics & anesthesia	30%

The outcomes of 2,608 births in 1979 were:

maternal mortality rate		0
neonatal mortality rate (babies	1000g)	0.42%
perinatal mortality rate (babies	750g)	1.45%
five minute apgar scores		98.3% 7-10

Stewart observes, "With a population of mothers at considerably higher than average risk, the midwives of North Central Bronx have achieved better maternal and infant outcomes than the rest of New York City, the state of New York in general, and the United States as a whole".[17]

One of the main reasons for midwifery's success in obtaining a high quality of maternity care, in addition to the practice of non-intervention, is the amount of time that the midwife spends with her client. Prenatal care is essential in maintaining a low risk status. The midwife provides a thoroughness of prenatal care that the physician cannot possibly match simply because of the time involved. In a ten minute visit, all areas of nutrition, exercise, family situations and support systems, psychological status, fears and concerns cannot be adquately addressed. Also, a strong bond of trust is necessary for a controlled birth process. If a woman does not feel at ease with her birth attendant tension develops, slowing down her labour. She exhausts herself thrashing about in pain and terror and resists her attendants during examinations. Although a physician may be deserving of his/her patient's confidence and trust, once again he/she is limited by time in his/her ability to develop a rapport.

One further question may be raised on the issue of safety and why one would choose a midwife. If physicians refrained from interfering with the birth process, and midwives were given medical backup, which of these two professionals would be better birth attendants? Considering the average training of a general practitioner in Canada and that of a midwife from a recognised school of midwifery, one has to ponder this question with some embarrassment. In her training, a midwife will usually witness several hundred births including abnormal ones such as malpresentations, breechs or twins. She is also required to do a minimum number of deliveries. In the Netherlands, for example, midwifery students must do at least fifty before they graduate. As far as I can ascertain,the average Canadian medical school does not have a minimum number at all, and a graduate may be lucky to have *observed* 50, let alone to have done any. University of Toronto graduates have the reputation of having excellent theoretical training but sadly, little practical experience.

Why Legalization is Inevitable

Although the main topic of discussion over governmental legalization of midwifery is optimal care and safety, it is probably economics and consumer demand that will ultimately form determining the need to change the present system of obstetrical care.

Economics, indicate that unless they are willing to cut back on their practices, physicians can not offer the consumer adequate time for optimal maternity care as previously discussed. Also, with the increasing insurance rates for obstetrical malpractice, many family practitioners are not doing deliveries anymore. Six years ago, the cost of medical malpractice insurance for obstetrics was under $100. This year it is $4900. A physician gets paid $15.30 for each prenatal visit, and $181 for an uncomplicated vaginal delivery. To just break even on insurance premiums, a family doctor must do at least ten deliveries per year. With many more deliveries, office hours are disrupted. With fewer deliveries, obstetrical care not only becomes economically unfeasible but skills become rusty as well. As a result, normal deliveries are being passed on to obstetricians. Obstetricians will soon be overwhelmed by the increasing numbers of patients and will have even less time to give to each patient. They may also be more inclined to apply costly high risk delivery techniques to low risk births. Midwives would reduce costs considerably in two ways. Firstly, they would receive a lower wage than obstetricians. Secondly, by virtue of their being specialists in *norma,* pregnancies trained to screen for high risk cases, the use of expensive equipment, procedures, nursing personnel, and anesthetists would be avoided in the majority of cases.

Consumer demand heavily influences the success of a new product or the drop in sales of an outdated one. More consumers of obstetrical care are seeking caregivers that are not only technically competent but will also offer them a sense of security and piece of mind derived from a trust that their wishes and rights will be respected at all times, especially at those times during birth when they are unable to speak for themselves. These consumers are not a minority fringe of radical-alternate-lifestyle-granola-grannies. They are well-educated middle to upper-class people who are used to researching, questioning and comparing the goods that they buy. And right now, they don't like what's available. Physicians who feel that these consumers are asking for unnecessary, selfish, luxury items are understandably vicious towards midwives. These physicians are either unable or unwilling to compete in the market place and are as a result losing their moonopoly. The fastest growing group of consumers in Ontario who are switching to midwives are doctors and nurses, a strong vote of confidencve for midwifery.

Consumer's Comment

1When talking to a classmate the subject of midwifery came up. His comment was, "I don't believe in it. It's not safe." This struck me as being rather an odd comment. I thought back to all the midwives I have worked with and one particular scene came to mind. It was of a stolid British midwife calmly coaching a trembling, sweat-drenched intern through a breech delivery. There was no obstetrician present because the intern had received the extenet of his obstetrical training and was considered fully competent to manage on his own. I hope for our sakes when we find

ourselves in similar situations, and for the sake of the woman entrusting the care of herself and her child to us, that the midwife will be there as a teacher, colleague, and friend.

REFERENCES

1. Devitt, N., How Doctors Conspired to Eliminate the Midwife, in Stewart & Stewart, ref. 38, vol. 2, pp. 345-370, 1979.
2. Ehrenreich, B., & English, D., Witches, Midwives, and Nurses, Feminist Press, New York 1973.
3. Barker-Benfield, G., Horrors of the Half-Known Life, Harper & Row, Colophon Books, New York, 352 pp., 1976.
4. Biggs, C.L., "The Case of the Missing Midwives." Ontario History. LXXV, No. 1, March 1983.
5. Wertz, R., & Wertz, D., Lying In - A History of Childbirth in America, Free Press, Div. of McMillan, New York, 280 pp., 1977.
6. J. Oppenheimer, "Childbirth in Ontario: The Transition from Home to Hospital in the Early Twentieth Century.", Ontario History, March 1983. Vol. LXXV, No. 1, pp. 54.
7. Kelly, S., et al., Birth Defects: Risks & Consequences, Academic Press, New York, 1978.
8. Kitzinger, S., Birth at Home, Oxford Univ. Press, Oxford, 154 pp., 1979.
9. Wegman, M., Annual Summary of Vital Statistics, Infant Mortalities in 25 Lowest Countries of 2 Million Population or More, United Nations Sources, J. Pediatrics, 64:6 Dec. 1979.
10. Physician-Oriented Medicare Care Shown to be a Negative Factor in Reducing Infant Mortality, NAPSAC News, 3:3:14, 1978.
11. Willson, J. Robert, Obstetric Care: The Effects of Consumerism, Post-graduate Medicine, March 1984, Vol. 75, No. 4, pg. 15.
12. Caldero-Barcia, R., "Some Consequences of Obstetrical Interference," Birth and The Family Journal, Vol. 2:2.
13. Chard, T. & Richards, M. eds., The Benefits and Hazards of the New Obstetrics, P. 147.
14. Levy, B., Wilkinson, F., & Marine, W., Reducing Neonatal Mortality Rate with Nurse-Midwives, Am. J. Ob. Gyn. 109:50-58, 1971.
15. Montgomery, T., A Case for Nurse-Midwives, Am. J. Ob. Gyn., 105:3, 1969.
16. Haire, D., Improving the Outcome of Pregnancy Through the Increased Utilization of Midwives, paper presented to the Blue Ribbon Commission on Infant Mortality, Washington, DC, February 14, 1980.
17. Steward, D., The Five Standards of Safe Childbearing, Napsac Reproductions, Marble Hill, 1981.
18. Haverkamp, jA., et al., The Evaluation of Continuous Fetal Heart Rate Monitoring in High Risk Pregnancy, Am. J. Ob. Gyn, 125:310, 1976.
19. Haverkamp, A., et al., Electronic fetal Monitoring Held No Better than Auscultation, Ob. Gyn. News, Jan 1, 1978.
20. Haverkamp, A., Does Anyone Need Fetal Monitors?, in Compulsory Hospitalization of Freedom of Choice in Childbirth?, Stewart, D. & Stewart L. (eds.), 3 vols. NAPSAC INT., 1979.

Patrons

The *Journal* staff and Medical Society wishes to thank the following patrons for their generous support.

Dr. Sharon M. Abel
Mrs. Elizabeth Akesson
Dr. Peter W. Alberti
Dr. E.C. Allen
Dr. Dominick Amato
Dr. Ulo Ambus
Dr. William Anderson
Dr. Crawford S. Anglin
Dr. John Armstrong
Dr. Maria Arstikaitis
Dr. Sylvia Asa
Dr. Mary Jane Ashley
Dr. Ronald Baigrie
Dr. Michael A. Baker
Dr S. Bandak
Dr Eric J. Barker
Dr. Jack Barkin
Dr. S. Barker
Dr. Marshall Barkin
Dr. Martin Barkin
Dr. Peter Barreca
Dr. Alan A. Bassett
Dr. Colin Bayliss
Dr. R. J. Benzie
Dr. John A. Beswick
Dr. Barbara Blake
Dr. Charles Brown
Dr. Peter Brueckner
Dr. Martin Buckspan
Dr. Gerald Burrow
Dr. David S. Byers
Dr. Paul Cameron
Dr. Lorie Cappe
Dr. John Cardarelli
Dr. D. C. Cattran
Dr. A. Cecutti
Dr. Abraham Chaiton
Dr. Catherine Chalin
Dr. Morris Charendoff
Dr. Albert T. Cheskes
Dr. R. J. Chisholm
Dr. Bernhard Cinader
Dr. Robert Cleghorn
Dr. Max M. Cohen
Dr. Alan W. Conn
Dr. George Connell
Dr. John Connolly
Dr. Harvey Coopersmith
Dr. Robert Corringham
Dr. Donald Cowan
Dr. Carol Cowell
Mrs. Marie Crookston
Dr. Donald Currie
Dr. Derek A. Davidson
Dr. John K. Davidson
Dr. Yvonne de Buda
Dr. Terence Doran
Dr. Dale Dotten
Dr. James Dubbin
Dr. James Duffin
Dr. Henry Durost
Dr. Robert Ehrlich
Dr. David Ellis
Dr. Stanley Epstein
Dr. Emmanuel Farber
Dr. Shim Felsen
Dr. Ronald Fenton
Dr. Joseph Fisher
Dr. R. Fleming
Dr. N. Forbath
Dr. Rodney Fowler
Dr. William Francombe
Dr. Jeremy Freeman
Dr. Arnis Freiberg
Dr. WW. C. F. Forder
Dr. Gordon Froggatt
Dr. A. E. M. Geisler
Dr. Robert Ginsberg
Dr. Richard M. Gladstone
Dr. David M. Goldberg
Dr. Melvyn Goldberg
Dr. Michael R. Goldberg
Dr. Barry Goldlist
Dr. Irvin Gollish
Dr. Maria Gospodarowicz
Dr. Avrum Gotlieb
Dr. Cameron C. Gray
Dr. David Greyson
Dr. Allan Gross
Dr. Joseph Gruss
Dr. Michael L. Guinness
Dr. Madhulika Gupta
Dr. Gordon Hardacre
Dr. Philip Halloran
Dr. Mitchell Halperin
Dr. & Mrs. Abraham L. Halpern
Dr. A. W. Ham
The Hanna Institute
Dr. Walter Hannah
Dr. Ian Harrington
Dr. Robert V. Harrison
Dr. Gerald Heasman
Dr. E. B. Hendrick
Dr. F. M. Hill
Dr. Charles Hollenberg
Dr. Robert Howard
Dr. Michael Howcroft
Dr. Shao-Nan Huang
Dr. Paul Hwang
Dr. A. R. Hudson
Dr. Robin Humphreys
Dr. Gordon Hunter
Dr. M. Hutcheon
Dr. R. H. Hyland
Dr. Aden C. Irwin
Dr. Mary V. Jackson
Dr. Robert W. Jackson
Dr. Christopher Jamieson
Dr. Moray G. Jansen
Dr. Romana Januszewska
Dr. Michael Jewett
Dr. Donald P. Jones
Dr. Albin T. Jousse
Prof. Nancy Joy
Dr. Armand Keating
Dr. John Kempston
Dr. Margot Kempton
Dr. Thomas Keogh
Ms. M. Kemptone
Dr. James H. Kerr
Dr. Edward Keystone
Dr. Jay Keystone
Dr. Hollister King
Dr. Jurgen Kontor
Dr. John Kostuik
Dr. Bernard Langer
Dr. Wolf-Dietrich Leers
Dr. S. L. Librach
Mr. Sidney Liswood
Dr. Lynn Loach
Dr. Frederick Lowy
Dr. John Lundon
Dr. Elliot Lyons
Dr. Robert E. MacDonald
Dr. Ross C. MacKay
Dr. Robert Lee MacKenzie
Dr. Susan Mackinnon
Dr. Stuart MacLeod
Dr. Ian MacNab
Dr. Aaron Malkin
Dr. Dina Gordon Malkin
Dr. Constantine Mallin
Dr. Jaanus Marley
Dr. Joseph Marotta
Dr. A. Bruce Marshall
Dr. B. J. Massouda
Medical Emergency Services Wellesley Hospital
Dr. Nancy McKee
Dr. Rosemary Meier
Dr. Kenneth R. Melvin
Dr. Peter Mingle
Dr. Charles A F. Moes
Dr. Keith L. Moore
Dr. J. E. Morgan
Dr. Heather Morris
Dr. David Murray
Dr. James F. Murray
Dr. Neil McAlister
Dr. David McNeely
Dr. Salim Naqvi
Dr. Constant Nucci
Dr. Richard Oglivie
Dr. D. Oreopoulos
Library Ortho Pharm
Ortho Pharmaceutical
Dr. Howard Ovens
Dr. Frederick Papsin
Dr. Robert Patten
Dr. George Alexander Patterson
Dr. Thomas Patterson
Dr. F. R. Pember
Dr. Gordon A Pengelly
Dr. Richard Perrin
Dr. W. J. Peters
Dr. Mel Petersiel
Dr. Annett Poon
Dr. Peter V. Poon
Dr. Kathleen Pritchard
Dr. John Provan
Dr. Vivian Rakoff
Dr. Anthony Rebuck
Dr. Robert N. Richards
Dr. Robin Richards
Dr. Kenneth Robb
Dr. Alexander Roberts
Dr. Robert Salter
Dr. Michael Schwartz
Dr. Arthur Scott
Dr Edward e. Sellers
Prof. Patricia Seyfried
Dr. Shao-Nan Huang
Dr. Robert H. Sheppard
Dr. Jerry Shime
Dr. Jack Shuber
Dr. K. H. Shumak
Dr. Ruth Shykoff
Dr. Daniel Silver
Dr. Harley Smyth
Dr. G. E. D. Snell
Dr. Robert Snihura
Dr. Isaac Sokinofsky
Dr. Marja Soots
Dr. Donald A Stewart
Dr Margaret Stoicheff
Dr. Robert Stone
Dr. Lorne Tarshis
Dr. Charles Tator
Dr. John Taylor
Dr. Ron Taylor
Dr. William Tucker
Dr. W. P. Unger
Dr. Joan Vale
Dr. Daniel G. Vaughan
Dr. Hillar Vellend
Dr. Malden Vranic
Dr. James P. Waddell
Dr. Paul Walfish
Dr. Gary D. Webb
Dr. R. K. Weber
Dr. Peter Webster
Dr. Richard Weisel
Dr. David Wesson
Dr. Catherine Whiteside
Dr. Robert H Wilkinson
Dr. D. R. Wilson
Dr. Daniel Wise
Dr. & Mrs. Manley S. Wolochow
Dr. Colin Woolf
Dr. John Zeldin
Dr. Walter Zingg
Alpha Laboratory
Boots Drug Store
Burroughs Wellcome Inc.
Ciba-Geigy Pharmaceuticals
Hoffman La Roche
MDICL Inc.
Medical Alumni Association
Medical Bookstore
Medical Mart Supplies
Merck Frosst Canada Inc
Novopharm Ltd.
Searle Pharmaceuticals
Squibb Pharmaceuticals
W B Saunders
White Cross
Cytopathology Associates
Med-Chem Laboratory

Infective Endocarditis: A Clinic and Pathological Study

Richard Upenieks, Jagdish Butany, M.D. FRCP (C)

ABSTRACT

Infective endocarditis is a serious infection of heart valves and endocardium caused by a microbiologic agent. Most often a preexisting cardiac anomaly is present but in 25-50% of cases no apparent underlying cardiac disorder is apparent.[7] The prognosis is strongly dependent on the virulence of the organism and, depending on the clinical setting, the management with antibiotic therapy coupled with surgical intervention.

It is important to bear infective endocarditis in mind when faced with a patient who has vague symptoms of malaise, low grade fever and tiredness. In both of the presented cases, infective endocarditis was either not considered at all or considered late in the course of the patient's disease. It is essential therefore to think of infective endocarditis in any patient who has acquired valvular heart disease, congenital heart disease or any cardiac prosthesis and presents with symptoms of pyrexia and malaise.

Introduction

With the advent of antibiotics, new sophisticated non-invasive diagnostic techniques, and a greater awareness of infective endocarditis, it was hoped that this acquired disease would disappear or at least significantly decrease in incidence. This has not occurred.[1] The greater use of invasive techniques, pacemakers, Swan-Ganz lines and more prosthetic valves being implanted appears to have counterbalanced the benefits of antibiotics and new diagnostic techniques. In addition, with an aging population and the recognition of unusual forms of infective endocarditis the mortality still remains very high, 31% and 71% for subacute and acute disease respectively.[1]

The most adverse prognostic indicator appears to be a failure to establish the diagnosis. Several studies reveal that the major cause of death is usually heart failure due to valve, leaflet or supporting structure destruction, or dehiscence of a bio-prosthetic valve. Early diagnosis may be helped if, when any patient with known heart disease (congenital or acquired) develops a fever of unknown cause that persists for more than a few days, blood cultures are performed before any antibiotic regime is started.[2] This condition must always be kept in mind and actively excluded early in the course of any illness rather than be thought of as a last diagnosis when nothing else proves correct.

Evidence of infection in the early stages may consist of no more than unexplained malaise, anemia, the insidious development of heart failure of no known cause, "rheumatic" aches and pains or even psychoneurosis.[2]

We present two case reports of patients who had infective endocarditis and died because of it in 1978 and 1985.

Case 1

A 75 year old man, a "university student", with no known valvular heart disease was admitted to the Toronto General Hospital after having been found on the floor of his room unresponsive. He was last seen 24 hours previously. There was a history of a CVA one year ago with no obvious defecits, however the patient was well until this acute event.

On admission, he was febrile (39°C), cyanotic with shallow respiration, cachectic and unresponsive. Blood pressure was 115/70 mm Hg and pulse 80 per minute. Cardiovascular examination revealed no murmurs. The lungs were clear and abdominal examination revealed no organomegaly. He had several pressure sores over his body and an ulcer over the right thigh (lateral surface).

His haemoglobin was 141 g/L (normal 140-148 g/L), white blood cell count 11.1 x 10^9/L (normal 4.0-11.0 x 10^9/L) and platelets were 137 x 10^9/L (normal 150-350 x 10^9/L). A left cerebrovascular accident was suggested by right sided hemiparesis and aphasia; the CT scan was normal. Because of neck stiffness, a lumbar puncture was performed revealing a clear colourless cerebro-spinal fluid with a blood cell count of 20 x 10^6/L, red blood cells at 7.0 x 10^6/L, glucose at 4.3 mmol/L (normal 2.7-4.1 mmol/L) and protein at 0.9 g/L (normal 0.15-0.45 g/L). Based on these findings, Ancef (1 g, I.V. stat Q6H) and Netilimycin (100 mg, I.V. stat and 80 mg Q8H) were started.

Over the next two days there was a period of initial improvement, followed by pyrexia, hypotension and later, peripheral cyanosis. His blood pressure dropped below 80 mm Hg systolilc. Platelets fell to 40 x 10^9/L and white blood cells to 5.0 x 10^9/L. Despite antibiotics he continued to deteriorate with developing severe respiratory distress and conjunctival petichiae. Blood cultures grew *Staphylococcus aureus* thus Cloxacillin (1 g I.V. stat and 1 g I.V. Q6H) was added to the antibiotic regime. Despite vigorous fluid replacement and antibiotics, the patient died with a clinical picture of overwhelming sepsis.

At autopsy, the heart weighed 510 grams demonstrating cardiomegaly and left ventricular hypertrophy. There was a 1.5 × 1.0 cm vegetation on the ventricular surface of the posterior mitral valve leaflet (Fig. 1 & 2). It was yellow-white in color, granular and coarse in appearance and surrounded several chordae tendinae. The flow surface of the posterior leaflet overlying the vegetations showed a 0.3 x 0.4 cm area of subendocardial hemorrhage. Histologically, these vegetations were those of infective endocarditis. The mitral valve showed myxomatous degeneration of both leaflets. Gram positive cocci were demonstrated on histological examination.

In addition, microabscesses containing gram positive cocci were found extensively in the left and right ventricular myocardium, kidneys, brain, right testicle, liver and spleen. Recent infarcts of the brain in the area supplied by the right middle cerebral artery, the spleen and liver, were also identified.

The respiratory system illustrated chronic bronchitis with bronchictasis and interstitial fibrosis. There was right lower lobe bronchopneumonia and pleural effusions of a total of 1800 ml were found.

The primary site of sepsis was probably the ulcer on the right thigh. The bronchopneumonia appears to be a recent

Figure 1 Mitral Valve Endocarditis
Figure 1 shows the left side of the heart with a mitral valve showing mysomatous degeneration. The posterior mitral leaflet shows a focal area of hemorrhage (open arrowhead). Underneath the leaflet is a friable mass (arrow head) with chordae tendinae "trapped" in it.

development. Death was due to staphylococcal endocarditis, numerous myocardial microabscesses and disseminated septis.

Case 2

A 57 year old man was admitted to Toronto General Hospital with a 2 day history of low grade fever and malaise. He had been on hemodialysis for 13 years because of glomerulonephritis, had one episode of Staphylococcal septicemia 2 years ago, and pericarditis one year ago.

About 6 months ago the patient noticed increasing fatigue and decreasing exercise tolerance. He used to be able to climb 2 flights of stairs fairly easily but was recently fatigued though not short of breath on climbing less than one flight of stairs. No orthopnea nor paroxysmal nocturnal dyspnea were reported.

Physical exam on admission revealed a pale, febrile (39 °C), distressed man with a "uraemic" tinge to his skin and a right conjunctival hemorrhage. His pulse was weak at 110 per minute and his blood pressure was 80/50 mm Hg. A left ventricular heave, loud pericardial rub and a harsh 3/6 ejection systolic murmur were noted. No diastolic murmur nor signs of heart failure were found.

Chest x-ray revealed clear lung fields, left ventricular enlargement and marked descending aortic calcification. Haemoglobin was 62 g/L, white blood cell count was 13.6 x 10^9/L and ESR was 68 Wintrobe units. Two consecutive blood cultures revealed Staphylococcal septicaemia and the patient was treated with Cloxacillin and Gentamycin. He was transferred to the Renal Unit for peritoneal dialysis to manage his electrolyte balance.

He remained mildly distressed and by the second day his fever had dropped to 36.5°C. However, his JVP was noted to be flat at the level of his clavicles and his blood pressure was 90/60 mm Hg maintained by plasma and saline infusions.

Subsequent chest x-ray revealed bilateral pleural effusions and a right middle lobe consolidation suggesting pneumonia. Staphylococcus aureus was still recovered from blood cultures and peritoneal diasylate. Gated nuclear angiography illustrated decreased wall motion in all segments with left atrial and ventricular enlargement. The ejection fraction was 35%.

By the second week the patient demonstrated marked deterioration with the major difficulty being the maintenance of a systolic blood pressure at 90 mm Hg despite aggressive volume expansion and dopamine administration. Eventual inability to maintain his blood pressure led to death.

The major pathological findings included end stage renal disease, infective endocarditis of the aortic valves (figure 3 & 4) and atherosclerosis of the aortra and coronary arteries.

Figure 2 Longitudinal section through the posterior mitral leaflet showing the friable vegetation (arrow head) and chordae tendinae (c) "trapped" in it. (M — posterior mitral leaflet).

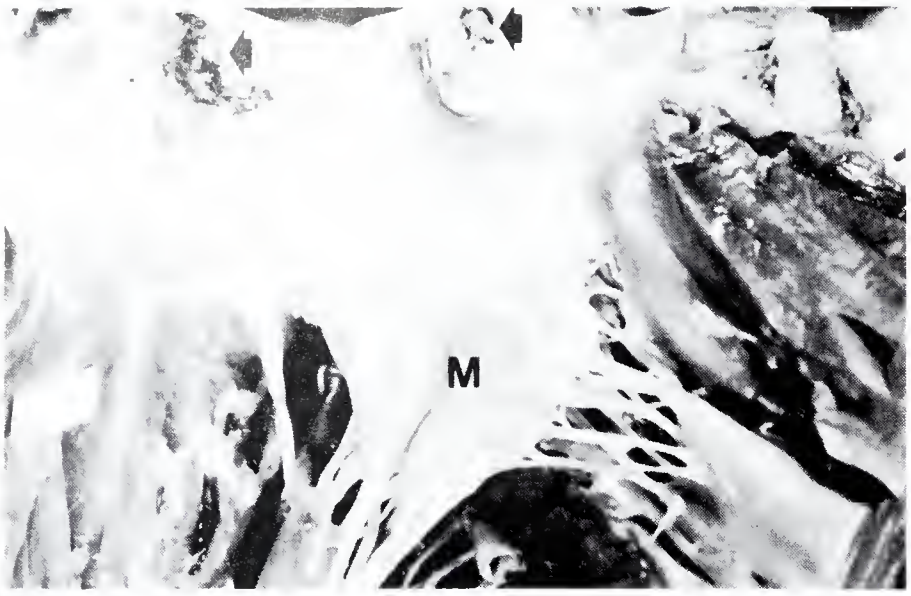


Figure 3 Aortic Valve Endocarditis
The non-coronary cusp shows friable, granular vegetation (arrow head). The cusp is perforated. The left coronary cusp also shows a small vegetation (arrow head). (M — anterior mitral leaflet).

The heart showed cardiomegaly (610 gms) with left ventricular hypertrophy and dilatation. The three aortic valve cusps were found to be fibrosed, thickened and extensively calcified. In addition, the non-coronary cusp showed friable vegetables and in the center a perforation associated with the endocarditis. An ulceration 6 mm in diameter was found on the ventricular aspect of the left coronary cusp and a small 2 mm haemorrhage was found on the free margin of the right coronary cusp. The resulting aortic insufficiency led to secondary chronic passive congestion of the liver and spleen, ascites and bilateral pleural effusion. Large splenic infarcts were seen and are believed to be secondary to the endocarditis, i.e. due to septic emboli from the aortic valve vegetations.

The kidneys weighed 25 grams each (normal = 150 grams each) and were markedly shrunken with multiple cystic areas. Associated secondary changes were hyperplastic parathyroid glands, adhesive pericarditis and renal osteodystrophy with dense osteosclerotic vertebral bodies. Uraemic neuropathy was illustrated by axonal and segmental demyelination.

Death is attributed to hypotension and low output cardiac failure, in an elderly person with calcific aortic valve disease, superimposed infective endocarditis with cusp perforation and heart failure.

Discussion

In the pathogenesis of infective endocarditis, consideration should be given to
1. the nature of the infecting organism,
2. the genesis of the thrombotic vegetations,
3. the distribution of the vegetations on the heart.

In both case reports presented, *Staphylococcus aureus* was the identified organism. In a recent compilation of 280 cases of native valve infective endocarditis over the years 1970 to 1982, S. aureus was found as the causative organism in 10% of cases.[3] However, in acute endocarditis, S. aureus is reported to be the predominant organism for outnumbering Streptococcus. [1 7] Overall, Streptococcus viridans continues to be the organism most frequently identified in 30% of native valve subacute and acute endocarditis.[3] Enterococci are reported in 18% of cases studied[3] and it is believed that these organisms will be more prevalent in the elderly because of more gastrointestinal abnormalities and because of the larger number of genitourinary procedures undergone by elderly men.[5] Of all organisms, Staphylococcus appears to be the most virulent. Native valve Staphylococcal endocarditis, in patients who are not intravenous drug abusers, has an associated mortality ranging from 25 to 40 percent.[5]

Infective endocarditis most often involves the left side of the heart valve where a greater haemodynamic load is present. Incompetent rather than stenosed valves are the preferred sites with the ventricular aspect of semilunar valves and the atrial aspect of atrioventricular valves being most commonly involved.[8] Endothelial injury and exposure of collagen from high pressure regurgitant jets of blood through incompetent valves promotes thrombus formation and organization. Circulating microorganisms may settle on damaged valves and induce further thrombus formation and possible systemic embolization.

Congenital heart disease continues to account for about 10% of cases of infective endocarditis while in adults rheumatic heart disease is still the major underlying disorder, currently found in about 25% of cases.[5] Over the past 25 years, the association of rheumatic heart disease with infective endocarditis has decreased from 40% to 25%.[5] This decrease of rheumatic fever associated valvular damage appears to be a major reason for the trend of infective endocarditis to be more common in older patients. However, a longer lifespan is associated with more degenerative valvular disease and this may be another reason for the increased incidence at a later age. Notable in case 1 was a myxomatous mitral valve. This is a degenerative valvular disease seen clinically in young women, as mitral valve prolapse and with an incidence of 5 to 7% in autopsy series in patients aged over 60 years.[6] It is considered to be the result of valvular collagen and elastic tissue replacement by myxomatous tissue with resulting mitral incompetence because of loss of leaflet rigidity.[7]

The distribution of lesions is generally reported as mitral valve 25-30%, aortic 25-30%, both mitral and aortic at 10%.[7] In one recent survey the distributions reported were aortic valve 50%, mitral valve 24% and both aortic and mitral at 14% of cases.[3] In the cases presented, one patient had mitral involvement and the other aortic but notable about the lesions was their local invasiveness which is not uncommon with virulent organisms such as the Staphylococcus.

The more virulent infections have been associated with ulcerations and perforations of the valve leaflets and extensions onto adjacent chordae tendinae, the valve annulus and papillary muscles.[6] In Case 1 the mitral valve had extensive myxomatous degeneration and it is possible that the infective endocarditis occurred because of this damage. However, the fact that most of the vegetations was situated on the ventricular aspect of the posterior mitral leaflet with several chordae trapped in it suggests that the predisposing condition may have been rupture of a chordae tendinae due to myxomatous degeneration. The ruptured chordae may then have provided a nidus for thrombus formation and colonisation by the Staphylococcus. *(cont. on page 52)*

Review
Doing Right: Everyday Medical Ethics

Solomon Papper M.D.

©1983, Little, Brown and Co.

Review by Kingsley Watts

Of the growing list of books on Medical *Ethics, Doing Right* is somewhat unusual. You will not find discussions of grand societal issues here - of the relative merits of abortion for example, or of euthanasia, nor of the growing dilemna of medical resource allocation. Instead, Dr. Papper, Head of the Department of Medicine at the University of Oklahoma, focuses directly on the sort of situations students an physicians face everyday. He begins with the thesis that not only are situations requiring ethical decisions common, they are often missed or ignored to the detriment of all involved. With this in mind his discussion is practical rather than theoretical in nature, aimed at increasing awareness and, hence, initiating personal behavioral change. It is this emphasis on behavior, on "doing right" as opposed to merely "being right", that is at the root of Dr. Papper's philosophy. As a basis for decisions he holds as self-evident several time-honoured precepts: do no harm; honour the patient's right to decide; and do unto others as you would have them do unto you. He then sets out to examine the notion of acting correctly, of doing right, both in our relations with patients, and in our other physician roles as well — teaching, learning, research, administration, and community health. It is, of course, an end towards which he assumes we all strive.

The distinction between doing right and being right is nowhere more evident than in patient care. Medical training, Papper maintains, tends to emphasize knowing the facts, making the right diagnosis. In Clinical Medicine, he argues, doing right, e.g. ordering a sputum exam and bronchoscopy for a patient with persistent cough, is more important than being right, e.g. diagnosing tuberculosis. Throughout the book the emphasis is on management rather than diagnosis, humility rather than acumen.

Physician's attitudes are a major source of doing wrong. The ill-effects on patient management of insensitivity, prejudice, loose talk, and impatience are discussed throughout the book. What may be regarded as problems of manners, of personality, gradually translate into moral issues — one does not have the right to act as one wishes when the way one acts interferes with care, and with our responsibilities.

Papper's emphasis on responsibilities, to our patients, to society, to our colleagues, and ultimately to ourselves, turns out to be central to his prescription for doing right. For the most part, they understandably involve concepts like honesty, integrity, commitment, etc. But in essence what they amount to is an oath, a pledge to consecrate one's life to the service of humanity — essentially the pledge doctors take when they graduate. Pappers sees it as a warning of sorts, taken prior to medical school, that is to be taken literally. His attitude is typified in the following passage:

> A respect for all human beings is presumably present in all of us; but that is not enough for physicians. In our work we have to learn *not* to judge the worth of a patient. Regardless of how respect for man is accomplished it *must* be accomplished.

Once again the importance is shifted from being right (knowing or saying that we must judge men equally) to doing right (actually treating all men as equals). It is not a question of whether we are or want to be like that, there is a moral imperative involved.

Acknowledging our all-too-human natures Papper offers such advice in the spirit of an ideal, a target upon which to aim one's sights. More importantly, he stresses that doing wrong is rarely something we decide to do. It has more to do with a lack of awareness, an insensitivity to the consequences of one's actions, than with any maliciousness of character. And it is with this insensitivity, or "dehumanization" as he puts it, that Papper is most concerned. At the risk of over-simplification, the struggle against this dehumanization is the central theme of the book. It can perhaps be summed up as a commitment to people above all.

Though hardly a novel idea, the implications are far-reaching; for losing sight of people above all leads to faith in other things; to faith in institutions; to faith in process; to faith in technology; to faith in efficiency, none of which, for Papper, have intrinsic value beyond their capacity to serve human ends. Losing sight of people above all leads to insensitivity; to phoniness; to overspecialization; to spanophilia (love of the rare); to the concept of the undesirable patient. Losing sight of people leads to dehumanization.

Papper sees it as an insidious process which he is determined to fight. Concentrating on the process of medical education he proposes, as a philosophic base for individuals and medical institutions alike, the concept of "human scholarship", a term which embodies concern for justice, compassion, and respect for scholarship. Above all, in students, teachers, and administrators the qualities of integrity, humility, and commitment to human scholarship must be sought. Concommitantly, the seeds of dehumanization must be eradicated — seeds that are imbedded in the very process by which we become doctors.

While the book does not claim to be a manual for the reformation of medical education, Papper's concern with the idea is clear. In his ideal school, prime importance is given to the quality of the teachers. He also proposes a large emphasis on formal ethical teaching and lists some of

the negative forces that he would see changed:

an overzealous curriculum; excessive numbers of examinations, especially in the first two years; too little relation to the clinical world in first year; preoccupation with grades and appeal processes; an atmosphere that is more like a continuation of an old-fashioned high school than the beginning of a learned and humane profession; and some abusive faculty.

It is a list that ought, perhaps to make us at the University of Toronto a little bit uncomfortable.

The real problems in medical care, Papper makes clear, generally arise not so much from any lack of factual knowledge on behalf of practitioners as from problems in attitude and approach. Information can always be learned or forgotten or become out of date. Behaviour, however, once adopted, is not so easily changed. Ultimately, of course, the struggle against dehumanization and toward doing right must be fought everyday within each and every one of us. The tools by which one fights are nothing new: they are constant vigilance, and self-discipline.

There is a tendency to recoil from such earnest idealism no matter how well intentioned or true it may be. And it must be confessed that there are times when Papper's pronouncements are self-righteously paternalistic. Nonetheless there are sage words and sound advice in abundance here. In providing practical advice it is the book's strength that Papper assumes the anecdotal tone of a man wishing to share with us his wisdom, his experience and his clinical judgement. What he lacks in philosphical rigor he makes up for in accessability. One may, no doubt, wish to take issue with many of his conclusions but it is well to remember that such is the nature of philosophy. Engaging in the discussion of moral dilemmas is assumed to play a part in the development of one's ethical awareness. And as such it is not always so much the answers as the process of seeking answers that is most important. Papper would be the first to agree. He regards the zealot whose opinions are set as dangerous.

What is ultimately most frustrating about the book, quite aside from a conspicuous lack of humour, is its looseness of structure, and its inconsistency of analysis. Largely a result of Papper's armchair-and-pipe approach the book is somewhat long on unsupported opinions and short on cogent arguments. As a source of practical ethical advice it is certainly worthwhile reading, but someone with an appetite for philosophical subtlety will likely put this 138 page book down and still feel hungry.

Doctors

Martin O'Malley

©1983, MacMillan Press

Review by Robert Mounsey

Doctors is a collection of vignettes centred on various doctors and their day-to-day experience in medicine. Each chapter contains a brief sketch of the life of a physician. The physicians chosen are eminent members of their fields and within their chapter an important aspect of their life is highlighted. The book is a completely Canadian product, with no shortage of exciting anecdotes by prominent doctors.

The prologue features an interview with Dr. Morton Shulman as he gives his views on doctors.

> "There's a terrible homogeneity in the medical profession, an awful dullness. In medicine you're going to find a tremendous similarity between a heart surgeon and a skin doctor. . . You're going to be amazed at how little difference there is."(p. 4)

The author, Martin O'Malley then promptly presents a series of chapters in which a heterogeneous and diverse group of physicians are found. A Vancouver radiologist is described who takes out the gallstones of the late Shah of Iran with an ingenious new technique. A holistoc doctor who believes that drinking your own urine can relieve allergic symptoms is examined in another chapter. Each chapter is completely different from the last with a new physician featured.

The book is very good at providing a quick tour through many different aspects of medicine. A doctor who specializes in the care and rehabilitation of doctors, who have suffered nervous breakdowns, is described. The stresses of medical school are examined and reasons proferred as to why some doctors turn to alcohol and drugs. Another chapter depicts two doctors who left Canada to open a practice in the United States. Thus, by changing the subject from chapter to chapter the book remains interesting.

A very obvious dichotomy exists throughout the book, on one hand doctors are depicted as average human beings going about their daily work. Many medical terms are demystified in the book and made intelligible for lay readers. However, this side of the book contrasts sharply with the very descriptive literary passages saluting doctors in their miraculous healing ability, unwavering commitment to excellence, and stoic manner in times of confusion. The statement.

> "At 8:55 a.m. Smyth shaves the top portion of the woman's head with a yellow handled disposable razor."

contrasts sharply with:

> "holding up his arms in a classical, priestly way. . ." (p. 12)

> "Neurosurgery is the most demanding of surgical disciplines. Its practitioners are subject to constant pressure, nearly always life and death." (p.15)

With the first statement the idea of the neurosurgeon using an ordinary shaving razor is portrayed. With the last two statements the idea of a miraculous superman is conjured up. This double image is a constant feature of the book. The reader is never sure in just what light the doctors are to be seen.

The book uses the doctors real names and discusses the hospitals at which they practice. By adopting this approach

it is impossible for any criticism of the doctors, or their institutions to be made. The only chapter that may be construed to even begin to show doctors unfavourably is Chapter 8. "When Doctors Err". In this chapter, malpractice is examined, but in the case presented, the complainants decide to sue the hospital, not any of the doctors.

> They . . . did not go after their family doctor. . . The doctor who treated Tony first was a stranger and the Yepremians did not go after him...Nor did they set their sights on the doctors who first treated Tony. And they did not go after the internist, . . ." (p. 157).

Maybe the author is trying to make the wry comment by entitling the chapter "When Doctors Err". The author may be hinting "When Doctors Err, Hospitals Pay."

The book, as mentioned earlier, deals only with the most distinguished members of medicine. Even the chapter that is supposed to deal with a medical student does this. The medical student collects rare books, has met Ernest Hemingway, and for seven years played pro baseball (probably just for fun). Is this a realistic picture of a medical student? By failing to explore the life of an average physician, showing his less glamorous tastes and rewards, the book misses an opportunity to capture the real glamour of medicine.

The book's treatment of Dr. Harley Smyth is superb. Details of his practice and professioinal life are explained thoughtfully, painting a realistic picture of what life is probably like as a neurosurgeon. The confllict between family and neurosurgery is emphasized. Both the first and last chapters are devoted to Dr. Smyth and his struggle to balance work and family obligations.

Doctors is a good book for a superficial sketch of some of medicine's elite. The format is such that before interest can be lost, a whole new character and scenario are encountered. One comes away from the book without being able to decide who was the intended audience. Was this book written for the doctors, featured, to wallow in self praise, for admiring peers, or for the lay public? Probably for each group as they read the book the answer to this question would change.

The Broken Brain: The Biological Revolution in Psychiatry

Nancy Andreasen M.D. PhD.

(Harper & Row Publishers, New York 1984)

Review by Pamela A. Stewart

In her preface to *The Broken Brain: The Biological Revolution in Psychiatry*, Nancy Andreasen describes this impressive work as "sharing its gestation with the birth of her first child". At that time, she was an English professor, "a humanist who knows quite a lot about the creative achievements of the human mind but nothing about the human brain and the body from which they derived". Operating from the Baconian dictum that "knowledge is power", she decided to pursue a greater understanding of the physiology, anatomy, and pathology of the mind and body. She achieved this in a more thorough way than a woman (or man) usually does when facing the mystery of the birth of her or his first child; she enrolled in medicine and eventually specialized in psychiatry. However, she has never forgotten her initial belief that knowledge indeed is power. This book is an admirable effort on the part of Dr. Andreason to share the power of her knowledge of the present changes in psychiatry with the lay-public. In her preface, she writes:

> I have felt ever since that ordinary readers deserve more intelligent efforts to translate the world of medicine and science into clear and readable form. Thousands, perhaps, millions of women wanted to know the same things that I did. Yet the only choice was between oversimplified and patronizing little pamphlets or the technical and arcane language of medical textbooks. I vowed that eventually I would try to write something better — the sort of book that I would have liked to read, something that conveyed the truth in both its good and bad aspects and yet avoided confusing and obscurantist jargon (p. vii).

Like all worthy medical books, designed for the lay-public, the ones who benefit best from the lifting of medical arcaneness, are the members of the medical profession. It was in this spirit that this book was extolled for its merits to me by a psychiatrist who thought it to be one of the best written books on psychiatry he had read.

Certainly, Dr. Andreasen has written an excellent piece of work. In it, she praises unabashedly the event of biological psychiatry and its attendent pharmacotherapy. I would argue that she explores the "truth" more in the light of "its good ways" than its "bad ways", but also would more than concede that she provides an excellent and optimistic synopsis of the newly emergent field of biological psychiatry.

She begins by giving an historical perspective on society's approach to mental illness. She discusses the misunderstandings that, as a result, shroud mental illness and cause reactions of "fear, embarrassment, shame and guilt" (p. 1). Indeed, she does not have to go too far back to find a time where mental illness was seen as "a punishment God gives to sinners, as a spiritual torment due to possession by the devil, or as a moral defect due to weakness of will" (p. 1). She argues how these beliefs have endured in some form in the 1980's, where we may no longer confine the mentally ill in chains, but we subject them to subtler forms of social stigmatism, cruelty and prejudice. She insists that this prejudice derives itself from a failure to recognize that mental illness is a physical illness "caused by biological forces and not by moral turpitude" (p. 2) just like diabetes, angina or cancer. This prevalent misconception leads the current mental patient to wear chains, just as confining, inescapable and painful as days of yore. Biological psychiatry, Dr. Andreasen states, removes the separation between physical and mental

illness and its resulting uneasy homeostasis, and places them in the same contingency as diabetes or heart disease. Moreover, she argues that, since psychiatric illness is perhaps the commonest type of morbidity in our society today, recognition of mental illness as a physical disease is necessary to alleviate the pain of stigmatism for a large section of society. She writes:

> Mental diseases are diseases that affect the brain, which is an organ of the body just as the heart or stomach is. People who suffer from mental illness suffer from a *sick* or *broken* brain, not from weak will, laziness, bad character, or bad upbringing. (p. 8)

Her argument is very alluring. Gone are the stigma, the shame of mental disease. Gone is the guilt that each parent faces when his offspring becomes mentally ill. But there seems to be a strange shift in semantics. Instead, of any effort to validate both psychological and physical disease as coming from the same spectrum of disease, and removing the anathema from pscyhological illness by removing the indignity of blame, physical illness is argued as the only acceptable modality of disease. Psychological disease is hence cast rather gratuitously as being physical, a disease of the brain.

Dr. Andreasen continues to persuade us, however, that biological psychiatry is the 'brave new world' of the future with a resulting final triumph over the mysteries of the mind. She goes on to provide an excellent summary of the three original schools of psychiatry: behaviorism, biological psychiatry and the psychodynamic model proposed by Freud. The biological model, itself, stems from Kraepelin and other psychiatrists and neurologists in the latter nineteenth and early twentieth century. Indeed, it is not a new movement as such, but an approach to mental illness that antedates Freud. The current pharmacotherapeutic approach to psychiatry is therefore a swing of the pendulum of medical fashion back to Kraepelin in view of the new discoveries in neurophysiology. Andreasen goes on to explain how the biological model or Kraepelian model can be applied to the four major syndromes in psychiatry today: schizophrenia, manic — depression, anxiety disorders and dementia. She backs her arguments both by data which locate some of these syndromes to specific parts of the brain, and by case-studies where patients were helped by pharmacotherapy or even surgical intervention. She describes these new discoveries in the "neuroanatomy" of mental illness as a "quiet revolution" where there is a slow, steady growth of fact upon fact over the past hundred years (p. 139). However, though Dr. Andreasen describes this "revolution" as a slow process of gathering knowledge and insight, she is quick to praise current psychopharmacotherapy as "wonder drugs". Though she outlines the possible side-effects of taking these medications, she also minimizes these effects. Similarily, when discussing the DSM III, her only criticisms are that it has not embraced the medical model wholeheartedly, and that it may have sacrificed usefulness for consistency. She defends the DSM III as a movement back to an "alliance with the mainstream medical tradition that emphasized the importance of careful definition of specific diseases based on symptoms rather than dynamics". (p. 158) But is Dr. Andreasen being overly optimistic? Is this not rather like Lucifer trying to make it back to the garden of Eden by reorganizing hell and palming it off as heaven? And does the DSM III as well as biological psychiatry deny the richness and complexity of the mind? Similarly, another question that haunted me on reading this work was that psychiatry was moving, perhaps, contrary to present scientific paradigm. Physics, for instance, now has moved closer to mysticism, dismissing Newtonian thought in favour of Einstein and Quantum theory. Is biological psychiatry, to continue this analogy, moving from quantum physics back to Newton, and forgetting in this effort the composite picture of the human being as physical body, soul/spirit and psyche.

Despite these shortcomings, Dr. Andreasen provides us with a thought-provoking and eloquent synopsis of biological psychiatry. The book reads smoothly like a superior work of fiction. Like good fiction, it is extremely worthwhile to read, but also like better fiction, I suspect it contains a literary dream which is only half reality.

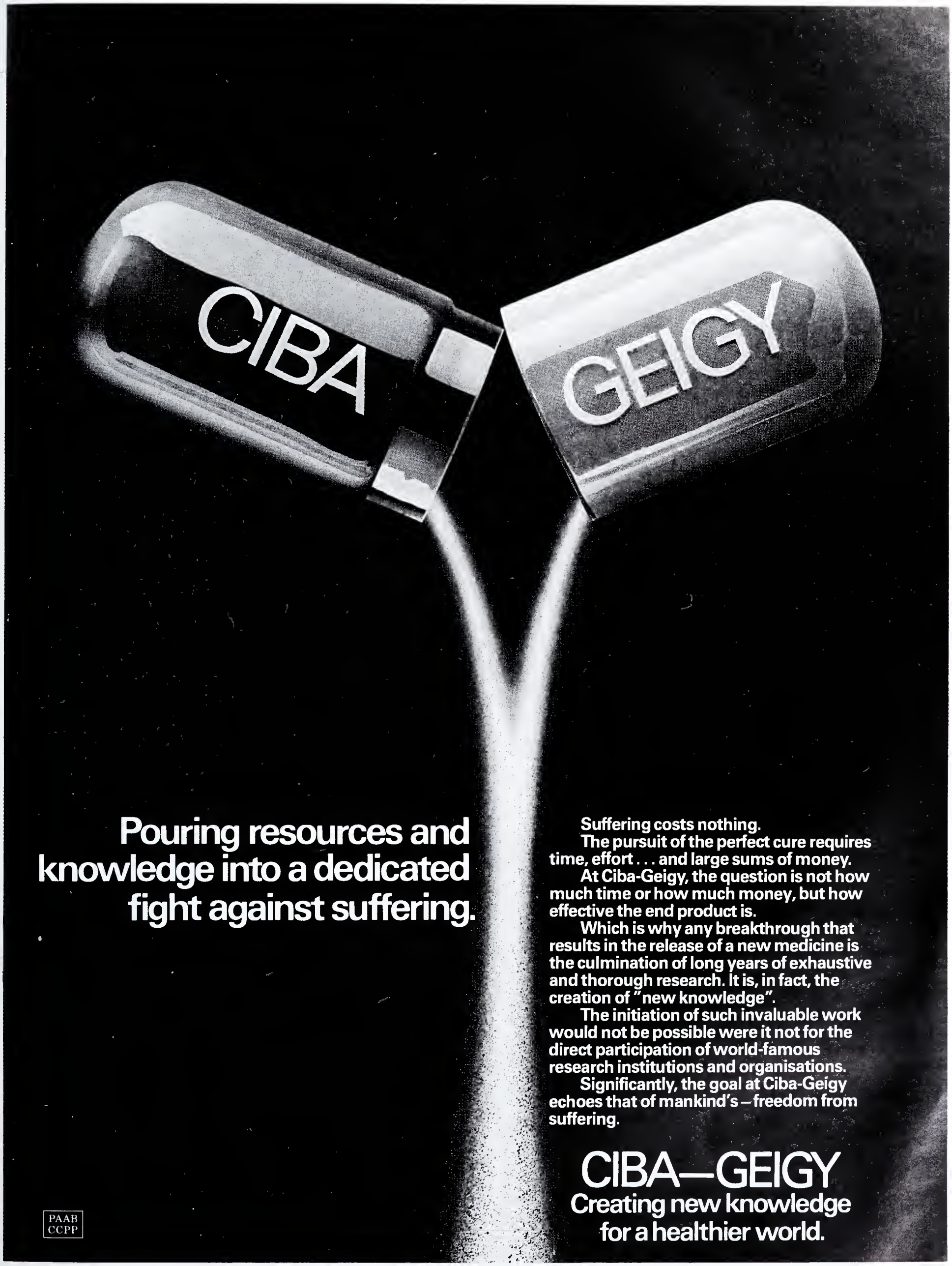
(Cont. from page 19)

63. Lohmann, D., Krug, J., Lampeter, E.F., Bierwolf, B. and Verlohren, H.J. Defect of suppressor cell activity and cell-mediated anti-beta cell cytotoxicity in Type I diabetes mellitus. Diabetologia: in press.
64. Sutherland, D.E.R., Sibley, R., Chinn, P., Michael, A., Srikanta, S., Taub, F., Najarian, J. and Goetz, F.C. Twin to twin pancreas transplantation reversal and re-enactment of the pathogenesis of Type I diabetes. Clin. Research 32:561A, 1984.
65. Dupre, J., Stiller, C.R., Gent, M., Jenner, M., Rodger, N.W., Wolfe, B.M., Von Graffenried, B., Heinrichs, D., Purdon, C. and Martell, R. Effect of ciclosporin on insulin secretion ;in recent onset Type I diabetes mellitus. In: Ciclosporin in autoimmune disease, ed. by Schindler, R., Springer, Verlag, Berlin, 1985, pp. 120-127.
66. Harrison, L. Diabetes mellitus. Proc. Can. Soc. Endocr. Metab. Vancouver, B.C., Sept. 9-13, 1985.
67. Addison, T. On the constitutional and local effects of disease of the suprarenal glands. In: A collection of the published writings of the late Thomas Addison, M.D., physician to Guy's Hospital, London, ed. by Wilk, S. and Daldy, T., New Sydenham Society, 1868, pp.209-239.
68. Josse, R.G. Autoimmune hypophysitis. In: Autoimmunity and Endocrine Disease, ed. Volpe, R. Marcel Dekker, New York, 1985. pp. 405-426.
69. Bottazzo, G.F. and Doniach, D. Polyendocrine autoimmunity: an extended concept. In: Autoimmunity and Endocrine Disease, ed. Volpe, R. Marcel Dekker, New York, 1985, pp. 375-404.
70. Nenfeld, M. and Blizzard, R.M. Polyglandular autoimmune disease. In: Autoimmune aspects of endocrine disorders, Academic Press, New York, 1980, pp. 357-366.
71. Irvine, W.J. Autoimmunity in endocrine disease. In: Advanced Medicine, Vol. 13, ed. Besser, G.M., Pitman, Tunbridge Wells, 1977, pp. 115-140.

(Cont. from page 48)

REFERENCES

1. Gossius, G., Gunnes P., Rasmussen K.: Ten years of infective endocarditis: A clinicopathologic study. ACTA Med Scand 217:171-9, 1985.
2. Goodwin, J.F.: The challenge and reproach of infective endocarditis. Br. Heart J. 54:115-8, 1985.
3. Malquarti V., Saradarian W., Erienne J., Milton M., Delahaye J.P.: Prognosis of native valve infective endocarditis: A review of 253 cases. European Heart Journal 5 (Suppl. C): 11-20, 1984.
4. Karchmer A.W.: Staphylococcal endocarditis: Laboratory and clinical basis for antibiotic therapy. The American Journal of Medicine 78 (Supl 6B):116-127, 1985.
5. Kaye D.: Changing pattern of infective endocarditis. The American Journal of Medicine. 78 (Suppl 6B):157-162, 1985.
6. Silver M.D.: Cardiovascular Pathology. Churchill Livingstone. New York: 1983, p. 103.
7. Robbins S.L., Cotran R.S., Kumar V.: Pathologic Basis of Disease, 3rd Ed. W.B. Saunders Co., Philadelphia:1984, p. 581.
8. Silver M.D.: Cardiovascular Pathology. Churchill Livingstone. New York: 1983, p. 525.



Pouring resources and knowledge into a dedicated fight against suffering.

Suffering costs nothing.

The pursuit of the perfect cure requires time, effort . . . and large sums of money.

At Ciba-Geigy, the question is not how much time or how much money, but how effective the end product is.

Which is why any breakthrough that results in the release of a new medicine is the culmination of long years of exhaustive and thorough research. It is, in fact, the creation of "new knowledge".

The initiation of such invaluable work would not be possible were it not for the direct participation of world-famous research institutions and organisations.

Significantly, the goal at Ciba-Geigy echoes that of mankind's – freedom from suffering.

CIBA—GEIGY

Creating new knowledge for a healthier world.

PAAB
CCPP

When you get there, will the cupboard be bare?

Major new drugs don't just appear. It requires a substantial research commitment to discover, develope and evaluate them. The five leading prescription drugs today did not exist ten years ago. Ten years from now, many leading drugs will be replaced by newer, more effective medicines. Major advances in drug therapy have been a significant factor contributing to the standard of health care in Canada. Drug research means a lot to our continued good health. And that's why Merck Frosst is a leader in Canadian pharmaceutical research.

MF CANADA

MERCK FROSST CANADA INC.

KIRKLAND, QUÉBEC

Where today's research becomes tomorrow's therapy